Pharmacology of the central GABA-ergic system

2020

László Köles

koles.laszlo@med.semmelweis-univ.hu

semmelweis.hu/pharmacology

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

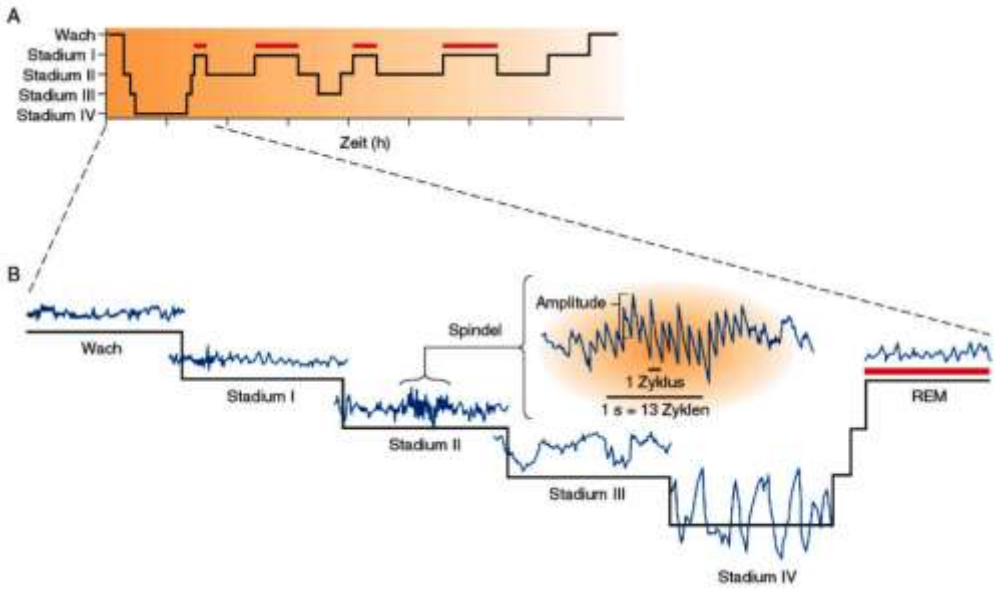
- reduction of anxiety without influencing motor or mental functions

Sedative effect

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

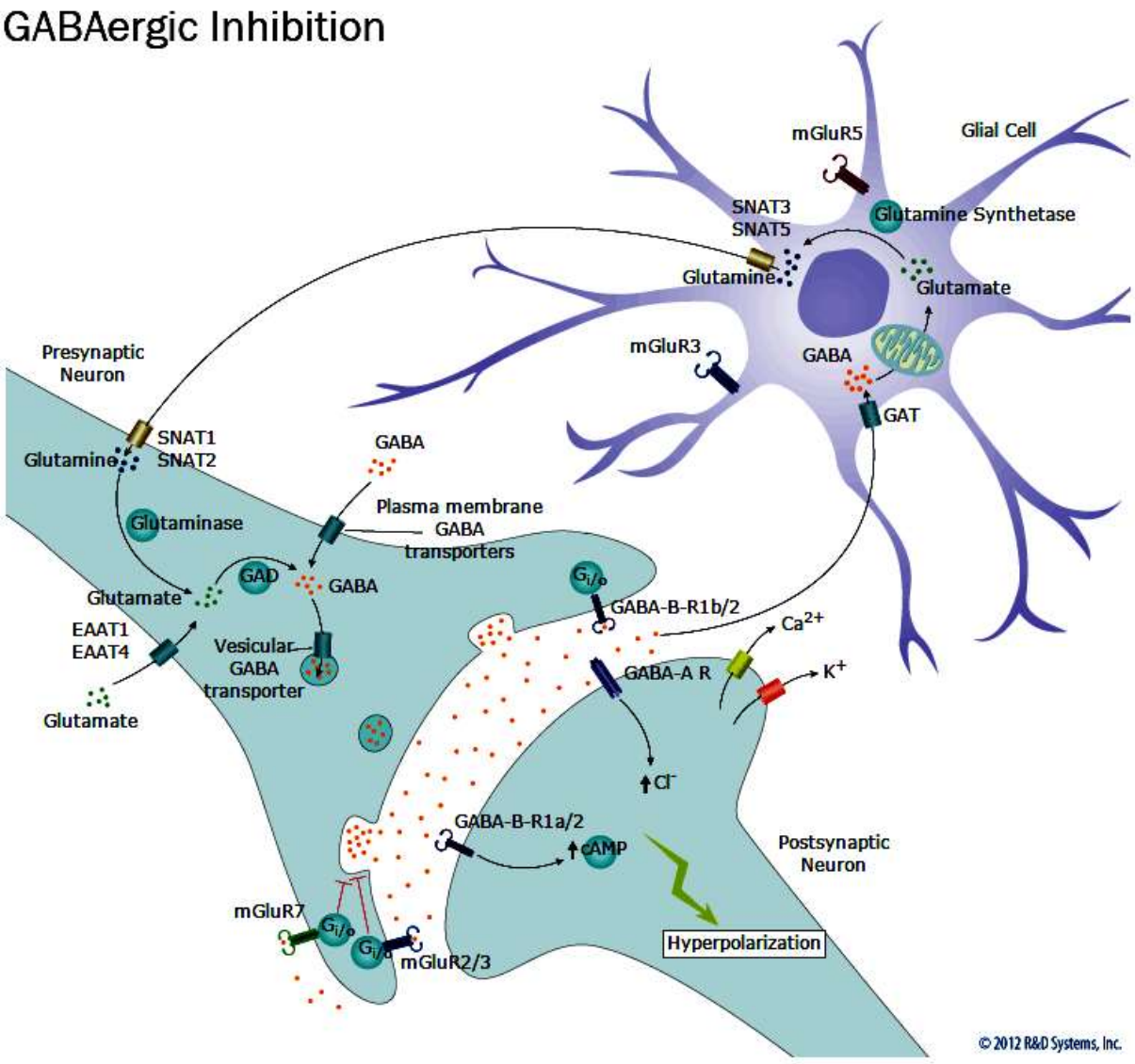
Hypnotic effect

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

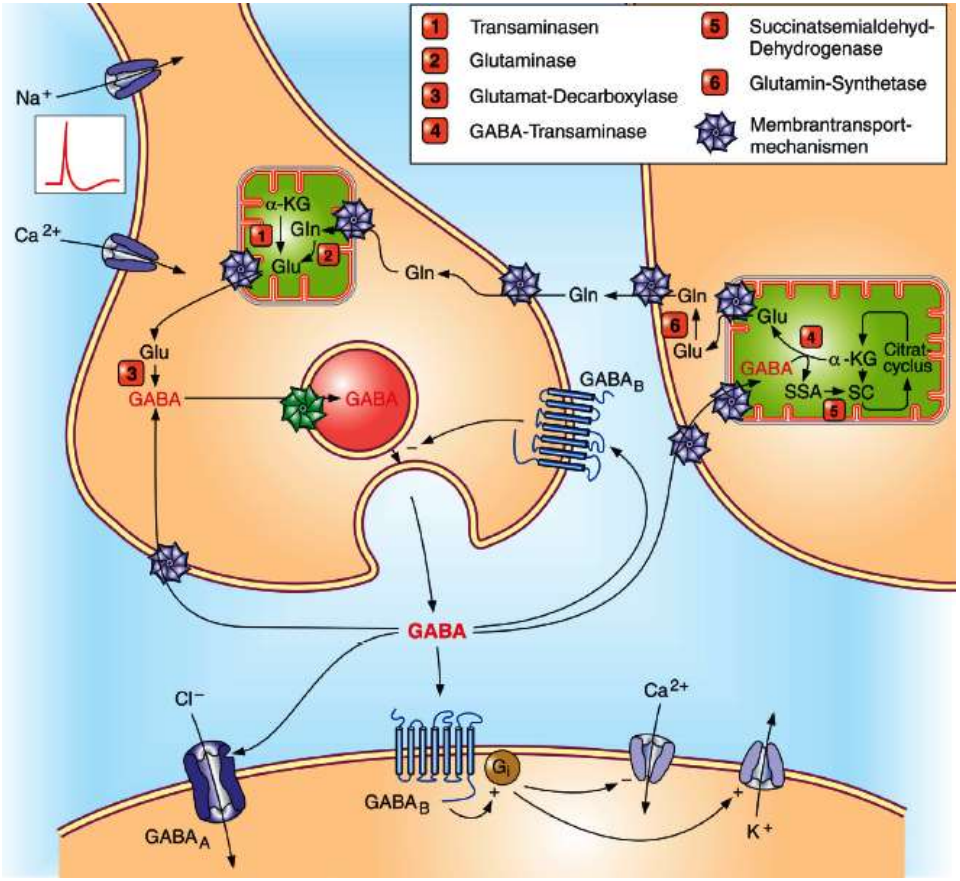


GABAergic neurotransmission

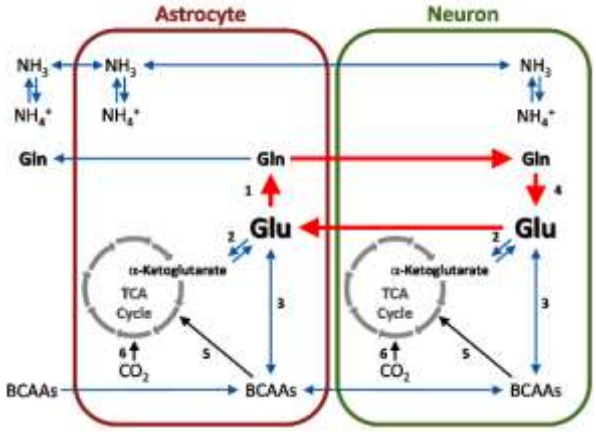
- **GABA – most important inhibitory transmitter in the brain**



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

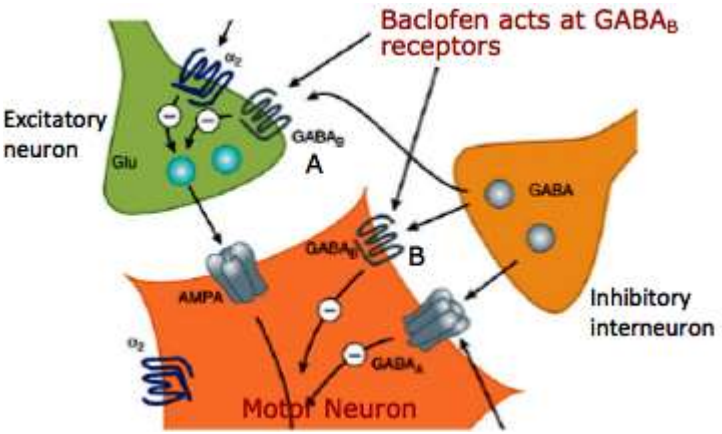
GABA receptors

- **$GABA_A$ (ionotropic)**
- **$GABA_B$ (G-protein-coupled)**

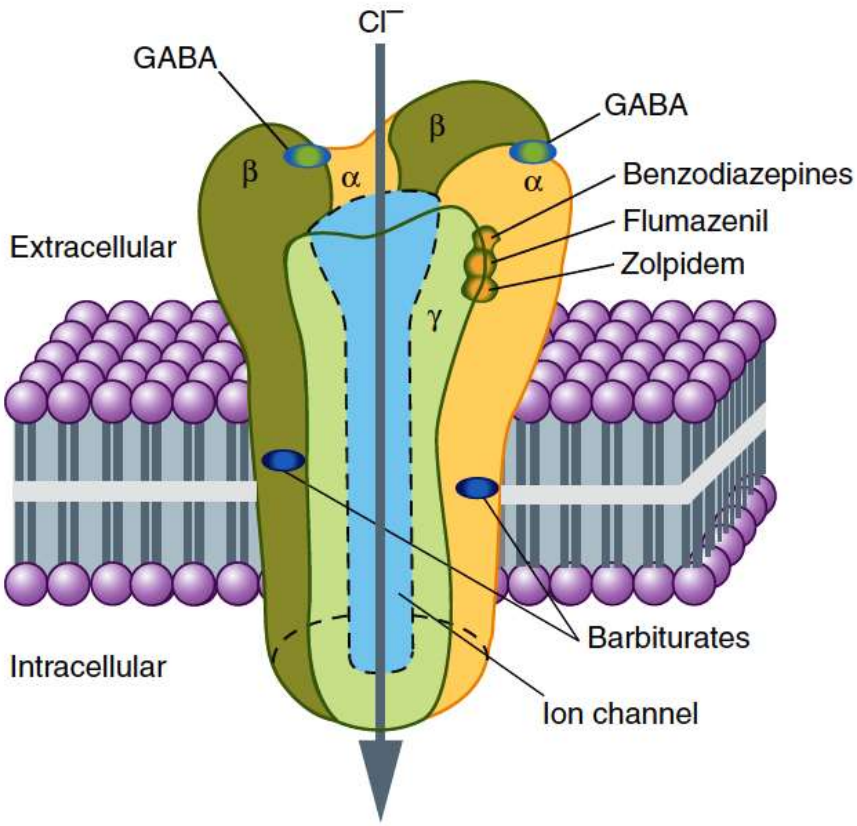
  - **$GABA_A$ receptors** are heteropentameric ligand-gated ion channels that permit the influx of Cl- ions to decrease membrane excitability. $GABA_A$ receptors mediate the majority of fast synaptic inhibition.
    $GABA_A$ receptors are extremely important pharmacological targets.

    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 distinguisable 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**

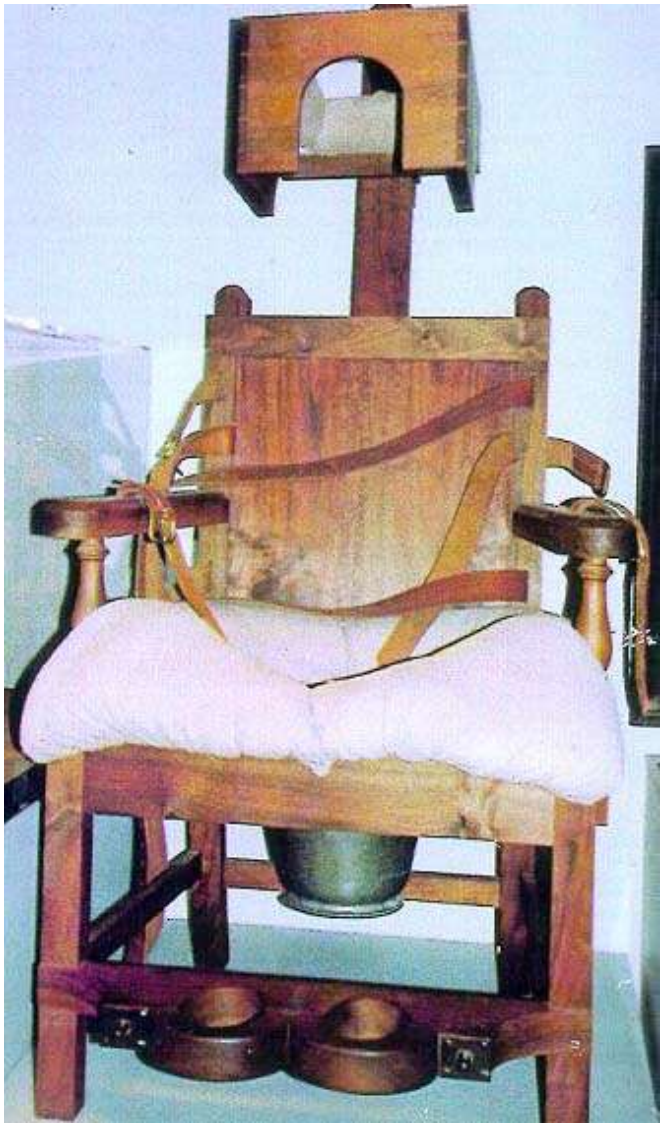
$GABA_A$ receptors
Subunit-composition and functional properties

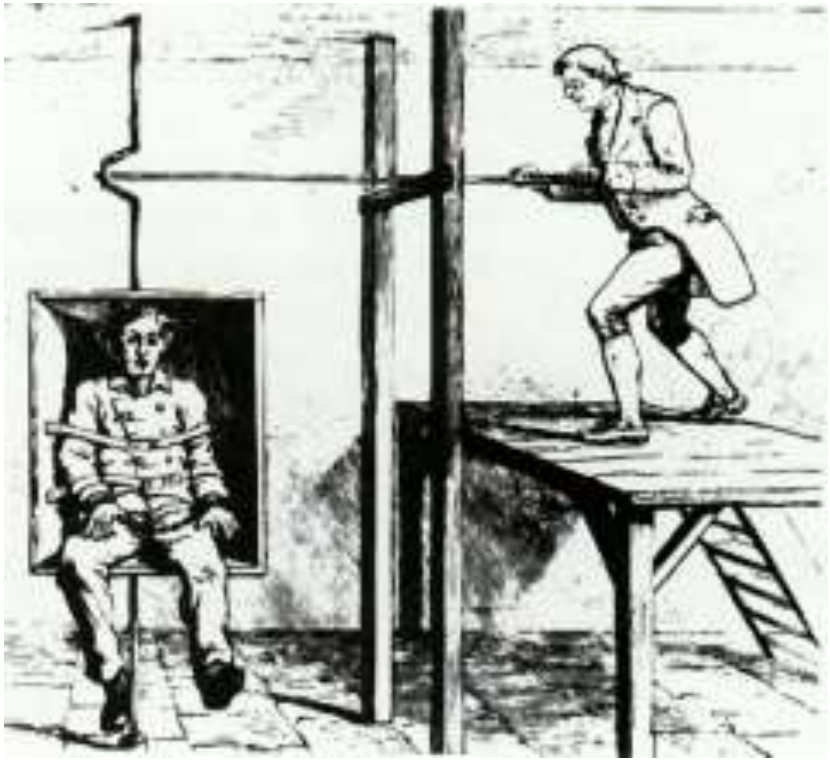
• **α-subunit – importance in pharmacological effects of the positive allosteric modulators**

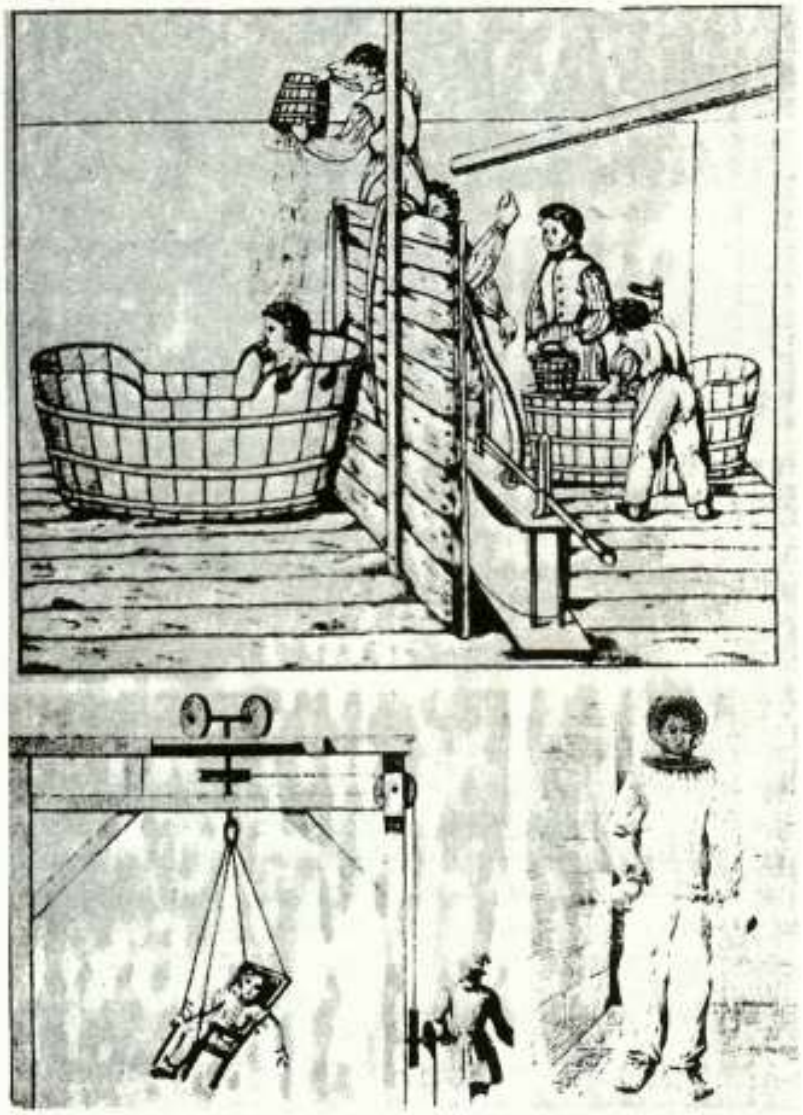
- **$GABA_A$-receptors with α_1-subunit – sedation, hypnotic effect**
  - **Z-hypnotics (zopiclone, zolpidem, zaleplon) - preferential affinity to binding sites at this receptor subtype.**
- **$GABA_A$-receptors with α_2-subunit – anxiolytic effect**
  - **Anxiolytic effects without sedation.**
- **$GABA_A$-receptors 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.

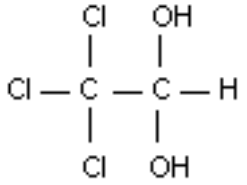
Noah became a man of the ground.
He planted a vineyard, drank wine and got drunk.
(Genesis 9.20-21)


LAUDANUM.--Poison
EACH FLUID OUNCE CONTAINS
45½ GRAINS OPIUM and 40 % ALCOHOL
U.S.P. TINCT OPII.
McCORMICK & CO., Baltimore, Md., U.S.A.

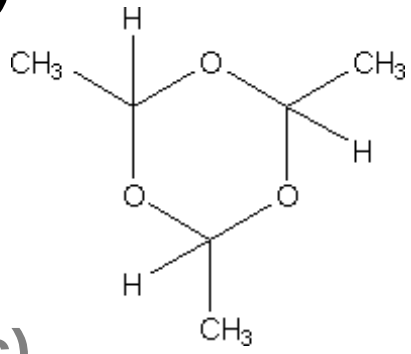
Valeriana (from the XVIth century)

Tranquillizers in the XIXth century

- **bromide**

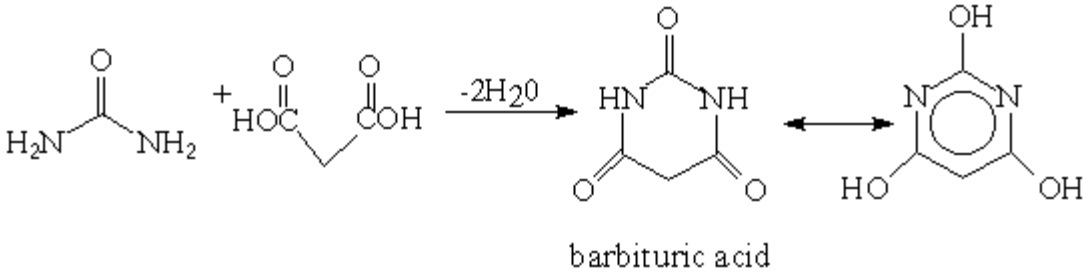


- **chloral hydrate (synthesis 1832, used since 1869, the first synthetic hypnotic)**
- **paraldehide (1882 – hypnotic)**



- **sulfonmethan (1888 – hypnotic)**
- **urethan (late 1800s – hypnotic)**

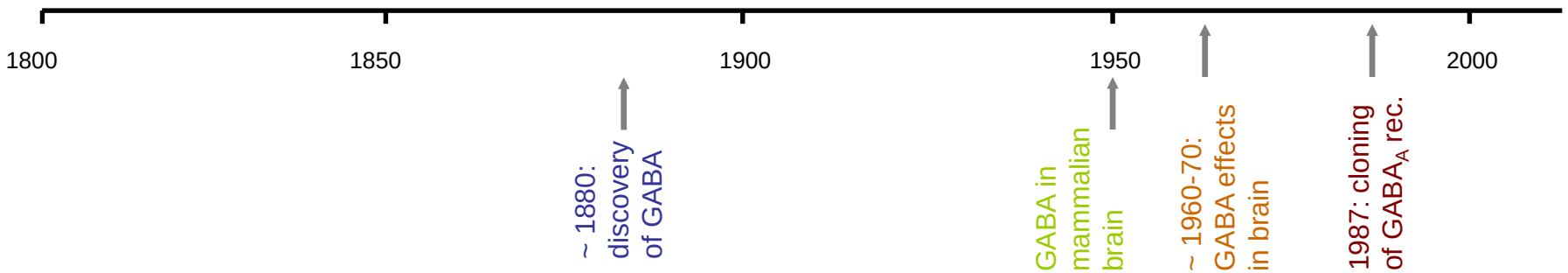
The beginning of the age of GABA: The barbiturates



- **barbituric acid – synthesized by Adolph von Baeyer 1864**

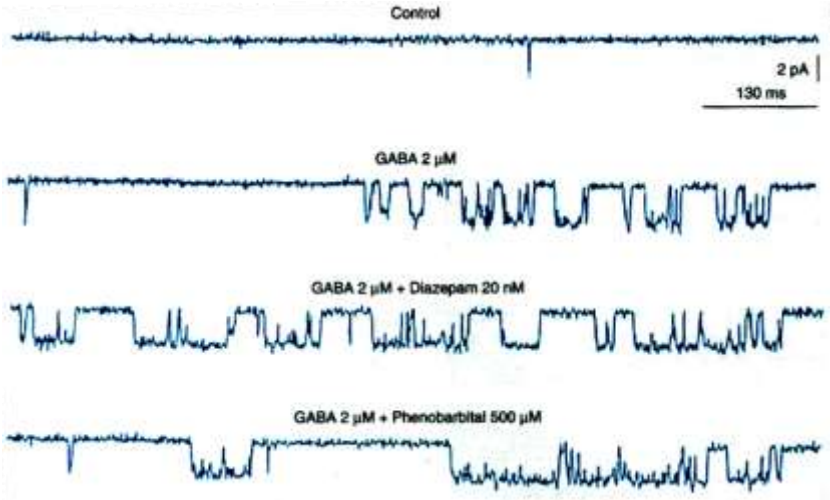
- **1903 – Emil Fischer, Joseph von Mering – the first barbiturates in therapy: diethylbarbituric acid (Veronal)**

1912 – Phenobarbital



Mechanism of action of barbiturates

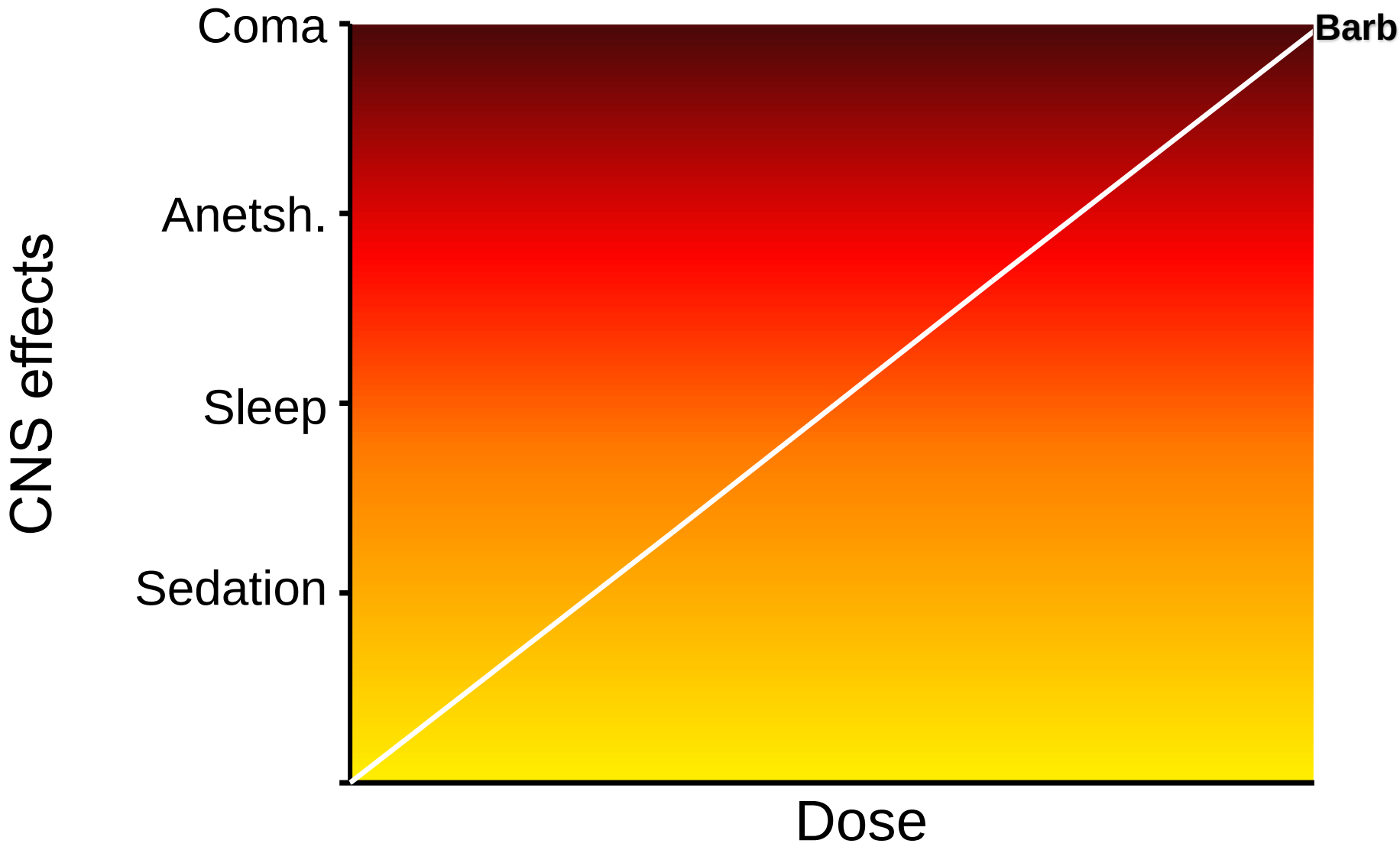
- They facilitate the actions of GABA by increasing the duration of the GABA-gated channel openings.



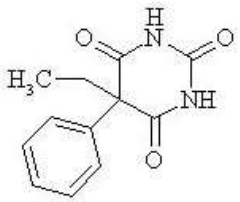
- At high concentrations they may activate directly the chloride channels.
- They might have further non-selective actions (depression of excitatory neurotransmission, nonsynaptic membrane effects).

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

BELBARB

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 galenical preparations of belladonna, such as the tincture, Belbarb *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 ¼ grain phenobarbital and the three chief alkaloids, equivalent approximately to 8 minims of tincture of belladonna.

Belbarb No. 2 has the same alkaloidal content but ⅓ grain phenobarbital per tablet.

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

Belladonna-alkaloids + Phenobarbital 1946

Phenobarbital 1954

whenever a patient needs
prompt, effective sedation...

short-acting

Nembutal®

(Pentobarbital, Abbott)

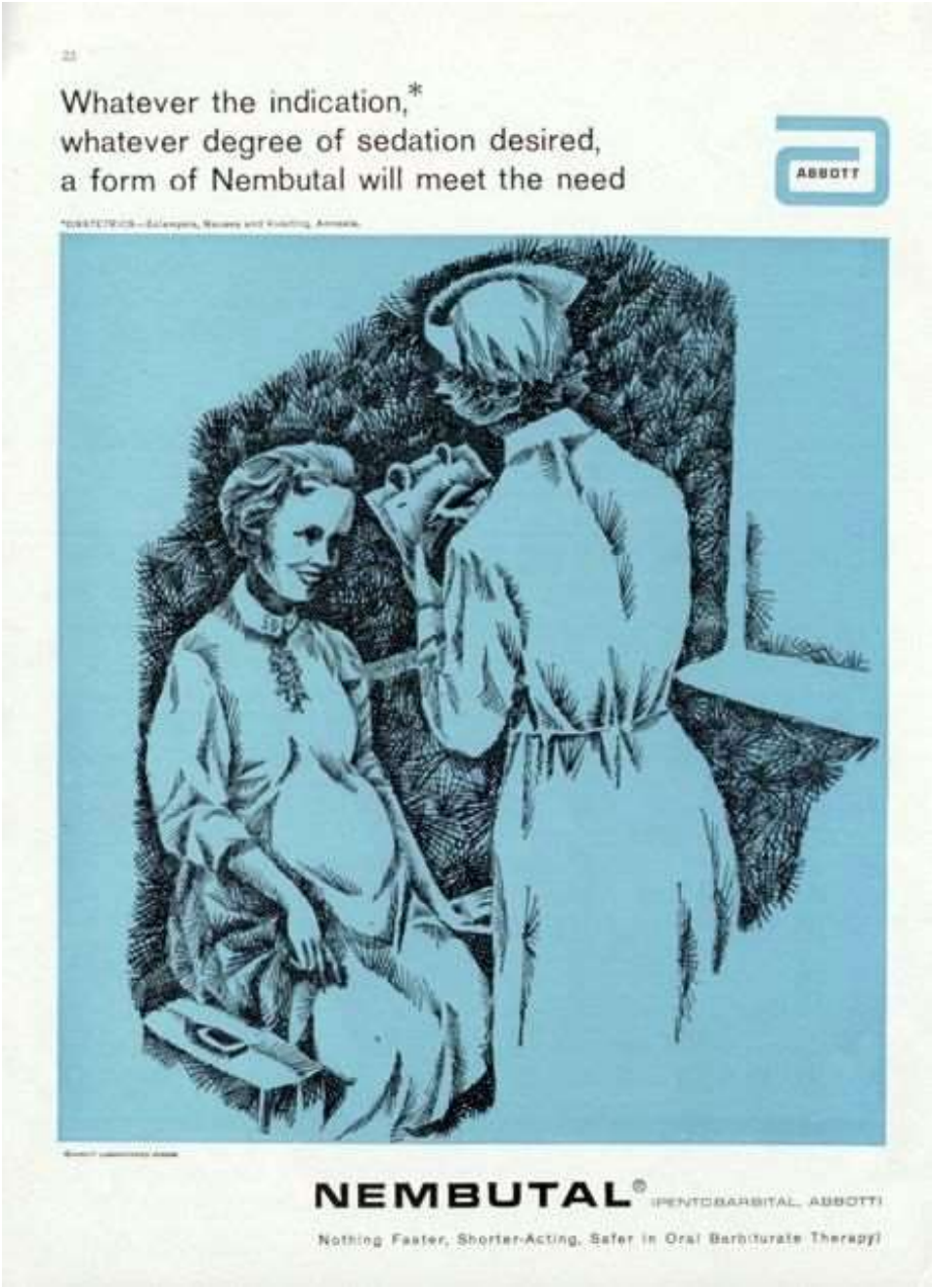
You can achieve any degree of cerebral depression using short-acting Nembutal—usually with only about one-half the dosage of many other barbiturates. This means:

. . . 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



Pentobarbital 1960

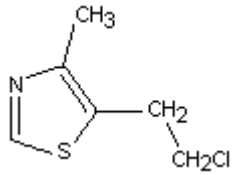
Metamphetamin + Phenobarbital 1959

Disadvantages of barbiturates as sedative-hypnotics

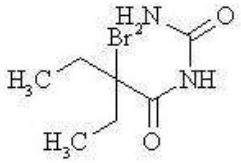
- **Low safety margin (intoxication is dangerous)**
- **No antagonist**
- **Psychologic and physical dependence, tolerance**
- **Enzyme induction, drug interactions**

Other sedative-hynotics in the barbiturate age

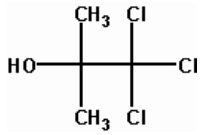
- chlomethiazole (1938)



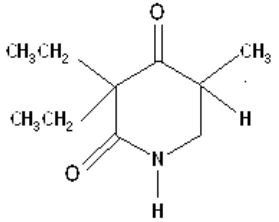
- bromisoval, carbromal (30's)



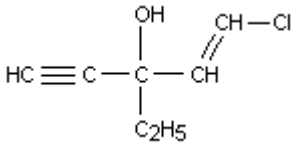
- chlorobutanol



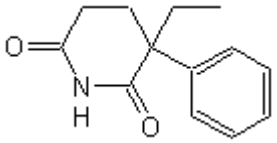
- methyprylone



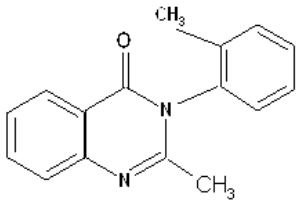
- ethchlorvynol



- glutethimide (1954)



- methaqualone (1955 – by product of malaria research)



BromuraL

Alphabromisovalerylcarbamide

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.

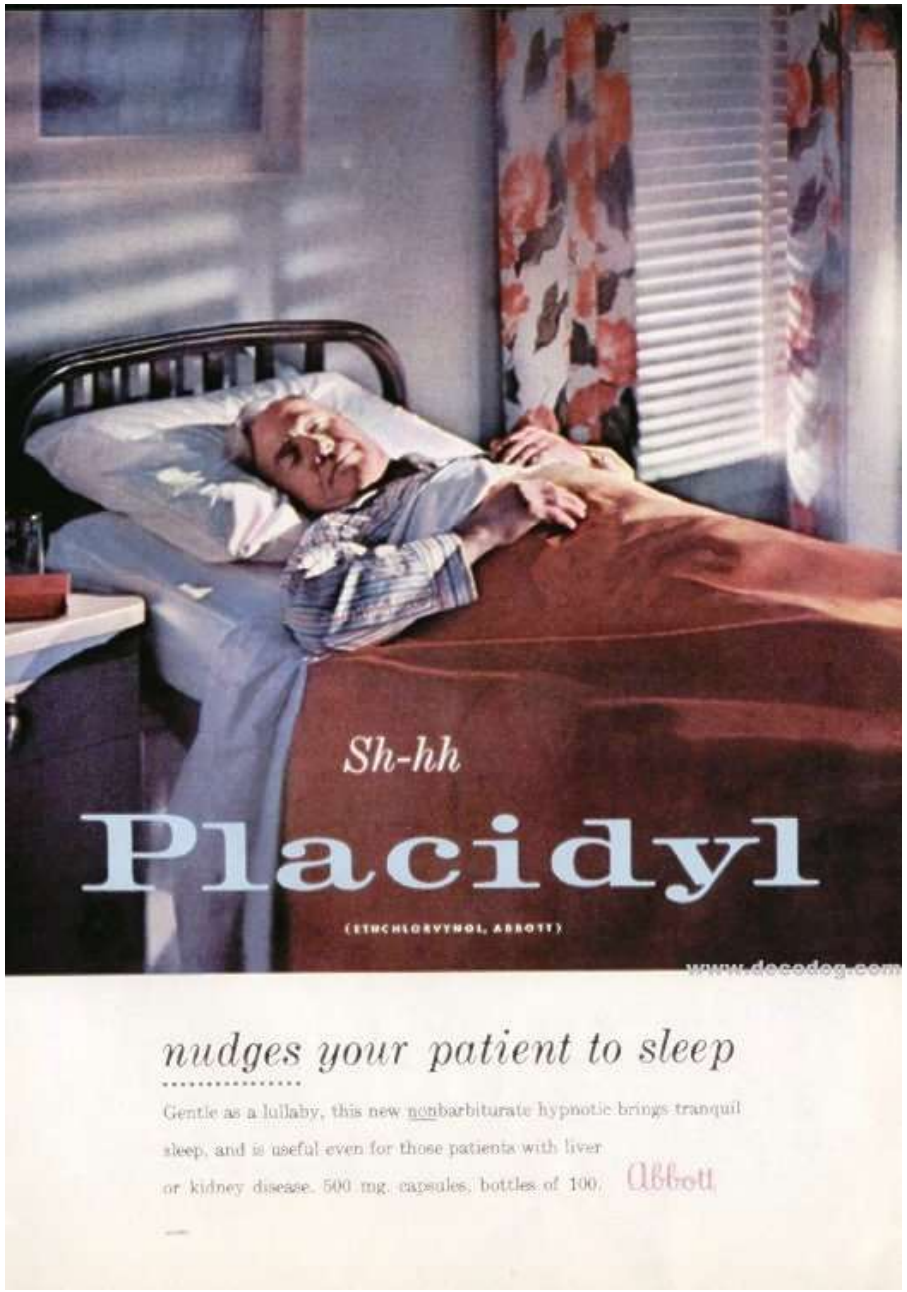
5 grain tablets and as a powder.

Samples and literature upon request

Bilhuber·Knoll Corp.,

154 Ogden Avenue, JERSEY CITY, N. J.

Bromisoval 1935



Ethchlorvynol 1956

why resumption of interrupted sleep is important to all your patients

12:45 a.m. Sleeping Easily

1:00 a.m. Interrupted

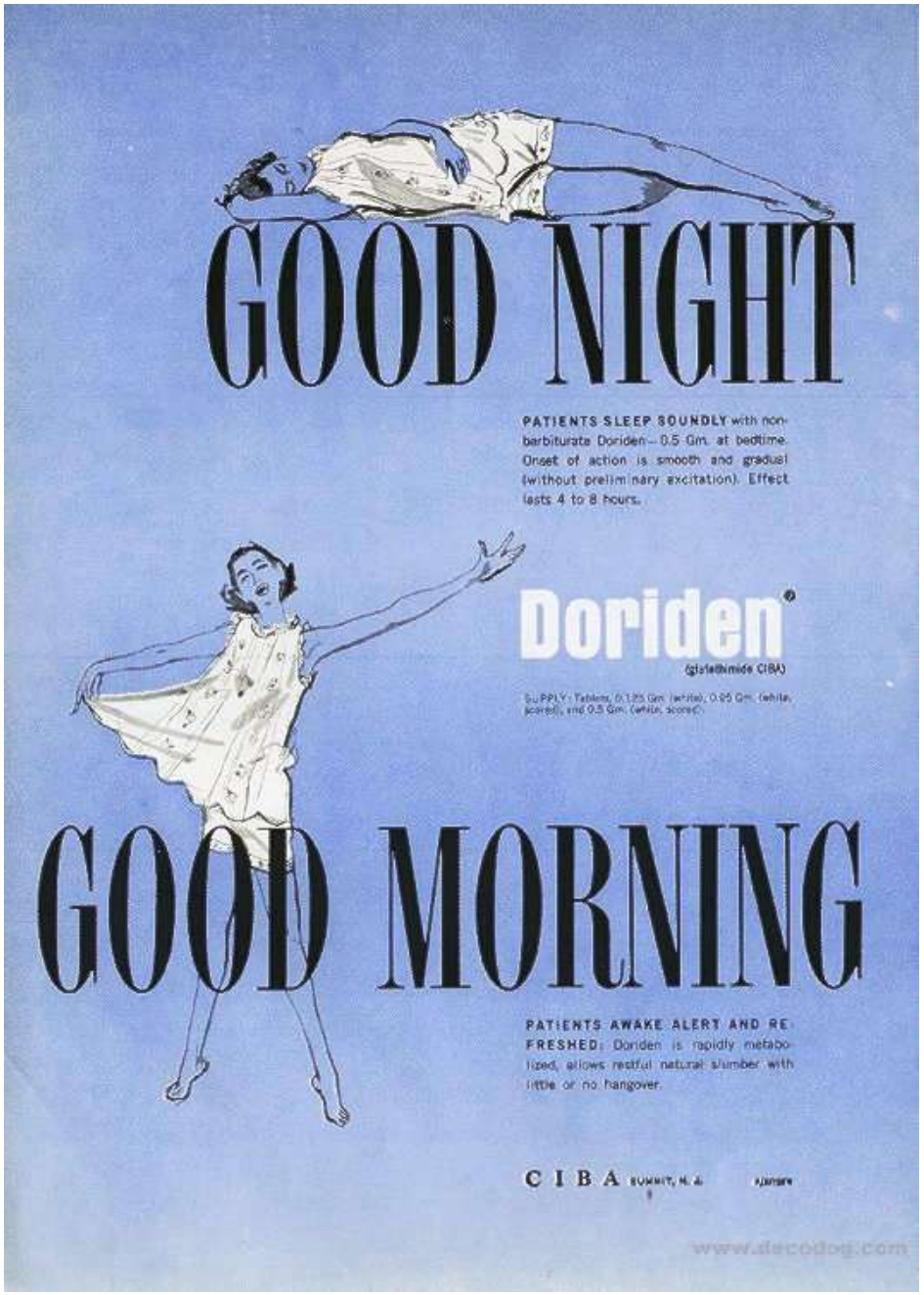
1:30 a.m. Rapid Resumption

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]

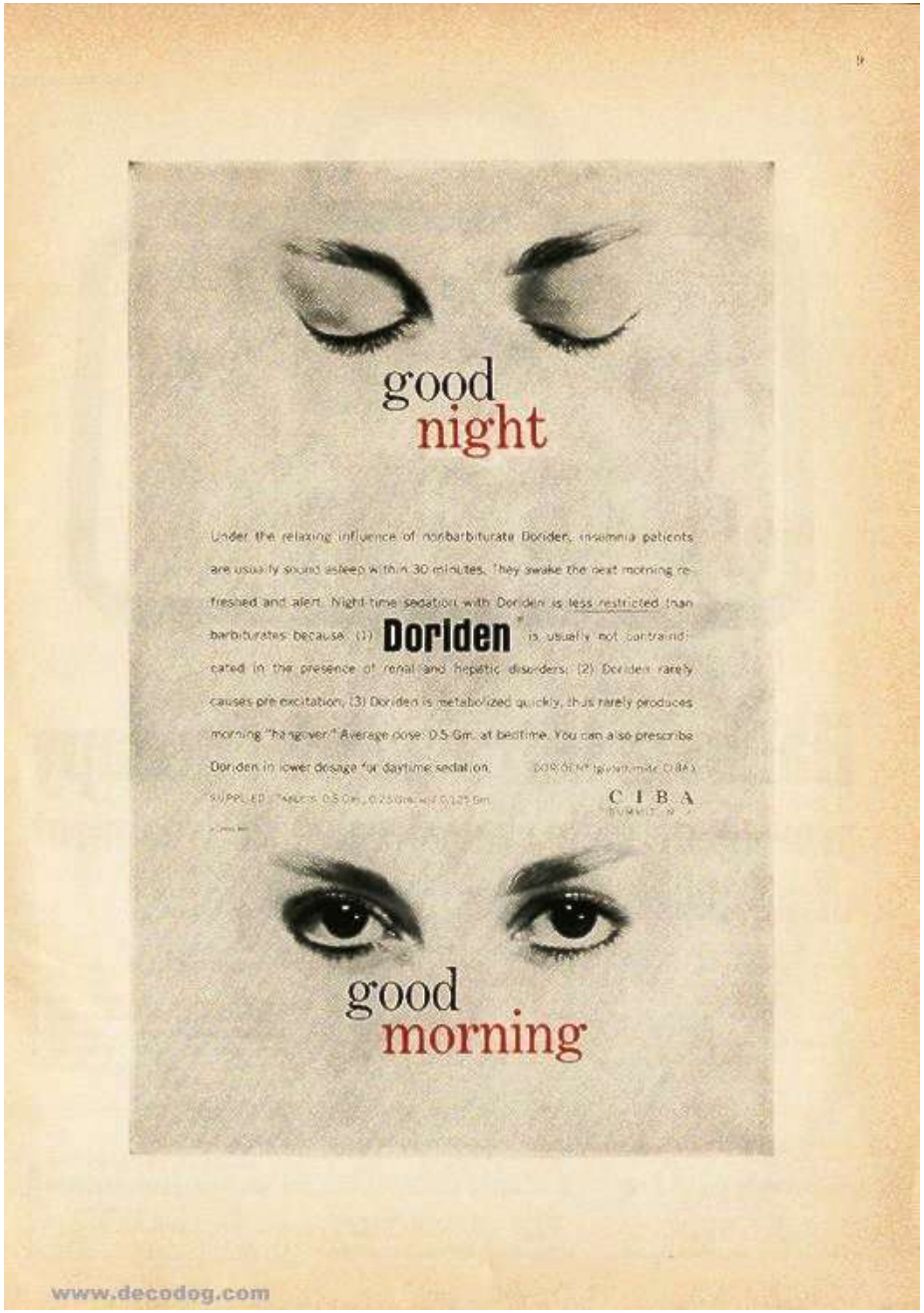
These qualities of resumption and refreshment set Quaalude apart from the drugs you may be using now. Quaalude induces a natural, physiologic sleep of 6 to 8 hours. And isn't that what you want for *all* your patients who need your help to a good night's sleep?
The secondary pharmacological actions of Quaalude—antitussive[4] and antispasmodic[5]—suggest that it may be especially useful in insomnias complicated by cough or gastrointestinal distress.
Consult product literature for complete information.

Quaalude™
(methaqualone)

Methaqualone 1956



Glutethimide 1957



Glutethimide 1958

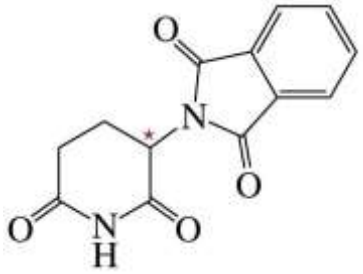
Mild and persuasive as a lullaby,
nonbarbiturate Placidyl gently lulls your
patients into refreshing slumber.
Brief and effective.
Prescribe it this week and see.

Abbott

Placidyl® nudges your patient to sleep

Ethchlorvynol 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 antiemetic 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?

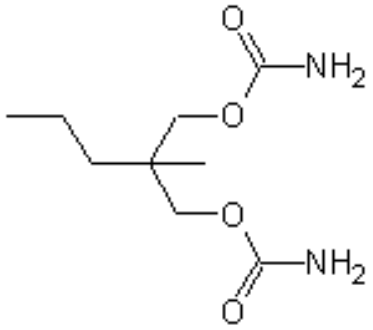
Hurstville, New South Wales. W. G. MCBRIDE.

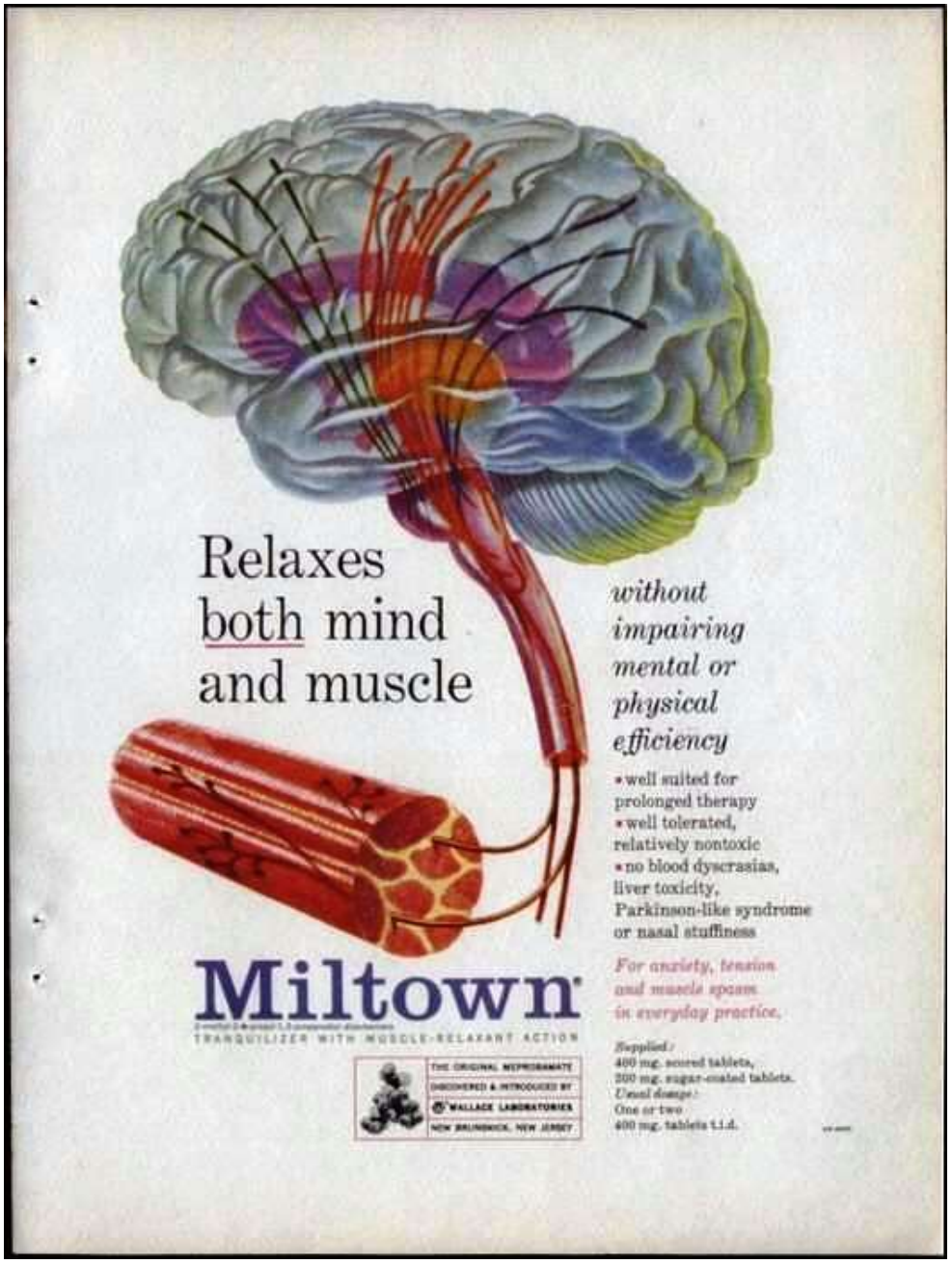
*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (' Distaval ') with harmful effects on the fœtus in early pregnancy ". Pending further investigation, the company decided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





Meprobamate 1958

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**