

# Să începem cu o simplă întrebare:

**Ce te mai poate  
învăța un  
bătrân  
anestezist,  
aflat de ani de  
zile la pensie?!**



# Oare știți povestea cu cei doi cocoși, unul tânăr și altul mai bătrân?!





# The history of intrathecal and epidural administration of opiates

*Gabriel M. Gurman and Silviu Brill*

Ben-Gurion University, Beer-Sheva, Israel

***[gurman@bgu.ac.il](mailto:gurman@bgu.ac.il)***

**Tg Muresh, December 2016**

Beer Sheva  
the center of  
Israel





# Ben Gurion University of the Negev, Beer Sheva-Israel





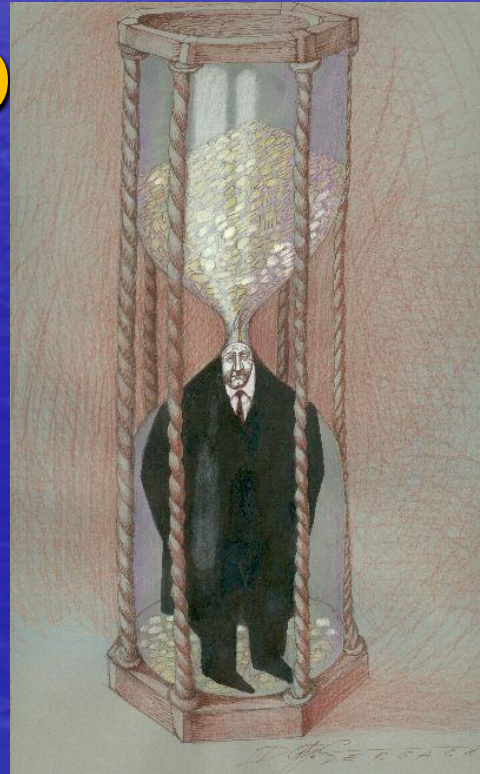
# The Faculty of Health Sciences- Beer Sheva





**Or one hundred years of  
clinical experience,  
promoting a technique  
with a slight chance of  
success.....**

**From Europe to USA and  
.....Japan**



# Îmi cer de la început scuze...

Istoria nu e  
întotdeauna  
captivantă,  
uneori e chiar  
plictisitoare,  
dar.....

- Cine nu are trecut, se pare că nici viitor nu are....





**Ceea ce vă pot promite  
e o scurtă întâlnire cu  
iluştri predecesori ai  
profesiei noastre  
dealungul timpurilor....**

**Just a short word,  
reminding everybody  
that the high rate of  
failures and  
complications of general  
anesthesia obliged the  
medical community in  
the 19<sup>th</sup> century to find a  
solution for surgical  
pain.....**





# **This essay deals with a multitude of aspects related to the use of opiates in “lumbar anesthesia”**

- **History of spinal and epidural anesthesia**
- **The first trial to use opiates in lumbar anesthesia**
- **A short description of the opiates history**
- **Sorry, no time for opiates receptors !!!**
- **A geographical glance on the story**

# The first hint



**Just one year  
before Morton  
ether  
anesthesia in  
Boston**

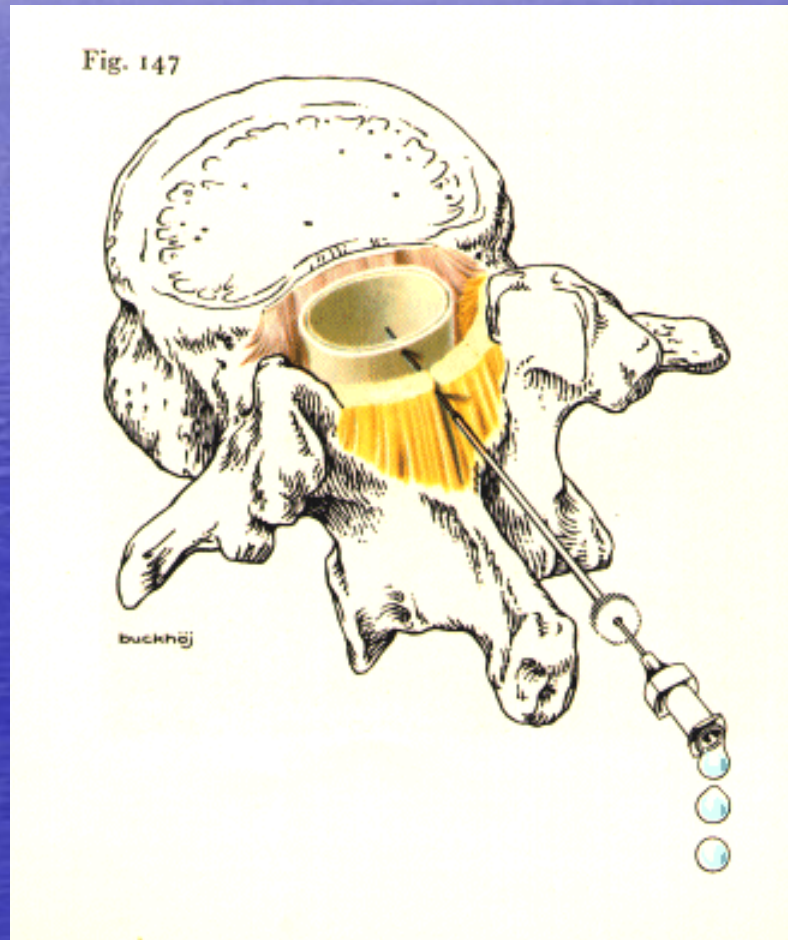
**Our story starts in the middle of 19<sup>th</sup>  
century**



# Francis Rynd

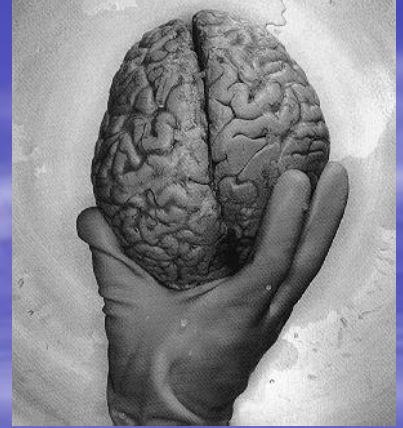
- Francis Rynd of Ireland in 1845 described the idea of introducing a solution of morphine in the neighborhood of a **peripheral nerve**, with intention of allaying neuralgic pain in that nerve.
- *Rynd F.: Neuralgia- Introduction of fluid to the nerve. Dublin Medical Press, 13:167, 1845*

# Intrathecal anesthesia





# First steps



- Hippocrates (470-400 B.C.), first spoke of “water of brain”.
- In 1692 Valsalva noted a watery fluid around the spinal cord of a dog.
- In 1764 Domenico Cotugno was the one who described the cerebrospinal fluid.
- In 1825 F. Magendie studied CSF circulation and named it.

*Bonica, J.J.:History of pain concepts and pain therapy. Semin. Anesth., 4:189-208, 1985*

# Lumbar Puncture



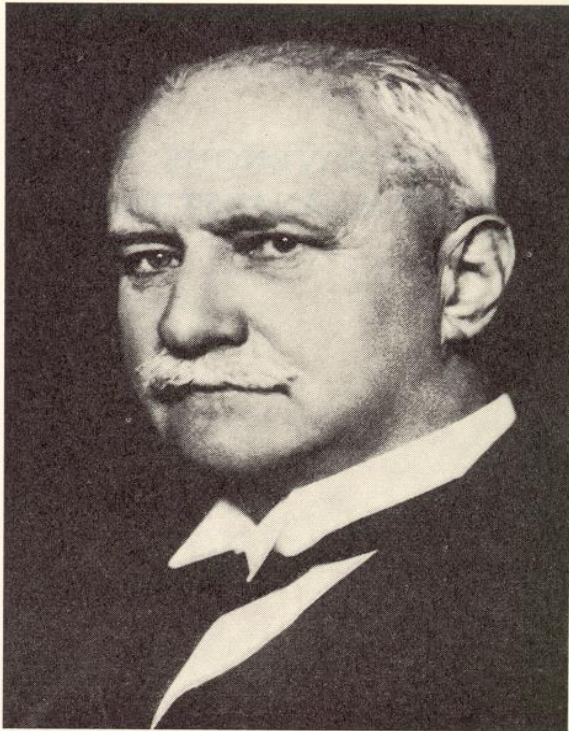
- Walter **Wynter** in England (**February** 1889) and Heinrich **Quincke** in Kiel, Germany (December 1890) independently introduced lumbar dural puncture.
- Because Wynter did not report these cases until **May** 1891 in Lancet, Quincke is usually credited with performing the first lumbar puncture.

*Wynter, W.E.: Four cases of tuberculosis meningitis in which paracentesis of the theca vertebralis was performed for the relief of fluid pressure. Lancet, 1:981, 1891*

*Quincke, H.: Die Lumbalpunktion des Hydrocephalus. Ber. Klin. Wochenschr., 28:929, 1891*



# ***August Karl Gustav Bier***



AUGUST BIER

\* 24.11.1861

† 12.3.1949

**SPINAL ANESTHESIA** •

Bier's Block - IVRA •

ARTIFICIAL HYPEREMIA •

THE TREATMENT OF •  
AMPUTATION STUMP

# Cocainization of the spinal cord



- August Bier theorized that his technique, he called “cocainization of the spinal cord”, might provide the necessary pain relief for major surgery.
- Bier and his assistant Hildebrandt gave **each other (!)** spinal anesthesia with cocaine on 16 August 1898 at Royal Chirurgical Klinik in Kiel.
- Bier had a certain amount of luck on his side; he worked at the same institution as Quincke and would have been familiar with his technique, and might even have borrowed his needles.



# **Rudolph Matas** and the unknown facts of history

- **Rudolph Matas of New Orleans , on November 10, 1899, was the first in the U.S. to apply the subarachnoid anesthesia with cocaine , B U T.....**
- **Matas may have been one of the first to inject morphine into the subarachnoid space (this is only a supposition)**

*Matas R. Local and regional anesthesia with cocaine and other analgesic drugs, including the subarachnoid method, as applied in general surgical practice. Phil Med J 1900;6:820-843*

# Thomas Jonnesco

- In 1908 Thomas Jonnesco and his assistant **Amza Jianu** of Bucharest, Romania, reported their experience with spinal analgesia at the Congress of the International Surgery in Brussels.
- The method was “too novel and to hearty” to be accepted without opposition.



Jonnesco T. La rachianesthésie générale. 1919 Edit Masson, Paris

Jonnesco T, Quatre cas d'analgésie par injection de cocaïne dans le sac lombaire. Bull Mem. Soc Chir. de Bucharest. II: 118-119,1900



LA  
**RACHIANESTHÉSIE**  
GÉNÉRALE

PAR

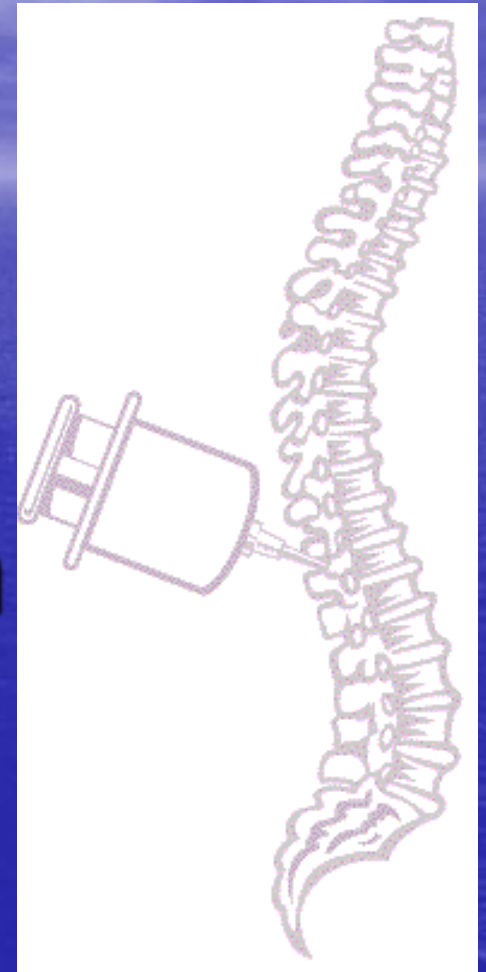
LE PROFESSEUR THOMAS JONNESCO

*Membre correspondant  
de l'Académie de Médecine de Paris,  
Ancien Directeur de l'École de Médecine de Bucarest.*

MASSON ET C<sup>e</sup>, ÉDITEURS  
LIBRAIRES DE L'ACADÉMIE DE MÉDECINE  
60, BOULEVARD SAINT-GERMAIN, PARIS, V<sup>e</sup>  
1919

**In 1919 Thomas  
Jonnesco  
published in  
Paris the first  
textbook of  
Spinal  
Anesthesia:  
“La  
rachianesthesie  
generale”.**

# Epidural anesthesia





# Leonard J. Corning

- In 1885, Leonard J. Corning (USA) performed the first epidural analgesia ...inadvertently. His intention was to treat..... masturbation.
- From his description of results and the manner of onset of anesthesia, there is little doubt that the result was...epidural anesthesia !!!!
- However he coined the term “spinal anesthesia”.

*Corning J.L. Spinal anesthesia and local medication of the cord. NY Med J 42:485, 1885*

# Fidel Pages Mirave

- In 1921, Fidel Pages Mirave of Madrid, a military surgeon, published the first report of lumbar epidural anesthesia. He called this new type of anesthesia “metameric anesthesia”.
- Unfortunately his practice was not disseminate to others, and his works was not translated into other languages.
- Pages were killed in 1923 in an automobile accident.

*Pagés, F.: Anestesia metamerica. Rev. Sanid. Milit. Argent., 11:351-365*





**Fifty years have passed  
till .....**

# Meanwhile.....

- **Anesthesia machine developed**
- **Tracheal intubation introduced in daily practice**
- **Artificial ventilation used**
- **Muscle relaxants became part of the usual pharmacological arsenal in OR**
- **Blood transfusion widely accepted**
- **Intensive care and Recovery rooms**



# Philip Bromage (1920-2013)

- In the 1950-1970 Philip Bromage (Canada) took the practice of epidural into the modern era.
- His book “Epidural Analgesia” published in 1978, played a pivotal role in the widespread acceptance and utilization of epidural analgesia in surgery, obstetrics, and pain management.



**Și acum la  
subiect.....**





# The history of medical use of opiates



# Papaver somniferum



- In the history of humanity very few substances have enjoyed such a prolonged and widespread use as the extract of *Papaver somniferum*.
- Its pharmacological effects were well known over 5000 years ago, when the Sumerians mentioned the poppy in their pharmacopoeia, calling it “Hu Gil” the plant of joy.
- According to Ebers Papyrus (c. 1534 B.C.E.) the Ancient Egyptians used “poppy” to relieve headaches, pain and provide anesthesia.



# Opium



- The word “opium” derived from the Greek “opus” which means vegetable juice.
- The use of opium for inducing analgesia during surgical operations is described in the records of the medical school of Salerno, in the 9<sup>th</sup> Century AD.
- In the 13<sup>th</sup> Century, **Boccaccio** mentions an opium potion in one of the novels of the “Decameron”.
- In the 16<sup>th</sup> Century, **Paracelsus** introduced Laudanum, a mixture of 10% opium in a hydroalcoholic extract, still in use today for the treatment of pain.

# Friedrich Serturner

In 1803, Friedrich Serturner, a German pharmacist, isolated an alkaloid of opium and called it **morphine**, from the Greek God of Sleep and Dreams: Morpheus.

*Serturner FWA, J Pharm fur Aertze und Apoth Chem, Leipzig 1806;14:17*





**Intrathecal  
and Epidural  
opioids (*că  
despre asta e  
vorba!!!*)**

- The first report of using opiates for spinal route belongs to **N. Racoviceanu-Pitesti** of Romania in 1900.
- On January 7<sup>th</sup> 1900 he injected morphine and cocaine for spinal anesthesia.
- Racoviceanu-Pitesti was invited by Tuffier to report his experience with spinal morphine analgesia at the Congress of the International Surgery in Paris (August 1900).



- In 1901 **Katawata of Japan** reported the injection of 10 mg of morphine and a local anesthetic into the subarachnoid space of two patients with uncontrollable back pain. The patients obtained excellent pain relief.

*Matsuki A, Nothing new under the sun – a Japanese pioneer in the clinical use of intrathecal morphine. Anesthesiology 1983;58:289-290.*

1901



**And once again in  
Romania, and once  
again in Bucharest,  
the capital, 70 years  
later.....**



# Pethidine

- Pethidine was the first synthetic opioid used to provide analgesia in humans.
- Eisleb and Schumann discovered its analgesic properties in 1939.
- **Nicolae Mircea** of Bucharest, Romania published the first report of using pethidine as the sole agent for spinal anesthesia in 1982. He reported a large series of 713 patients who received intrathecal pethidine for abdominal surgery.

*Mircea N, Constantinescu D, Jianu C et al, Anesthesie sous-arachnoidienne par la pethidine. Ann Fr Anesth Reanim 1982;1:167.*

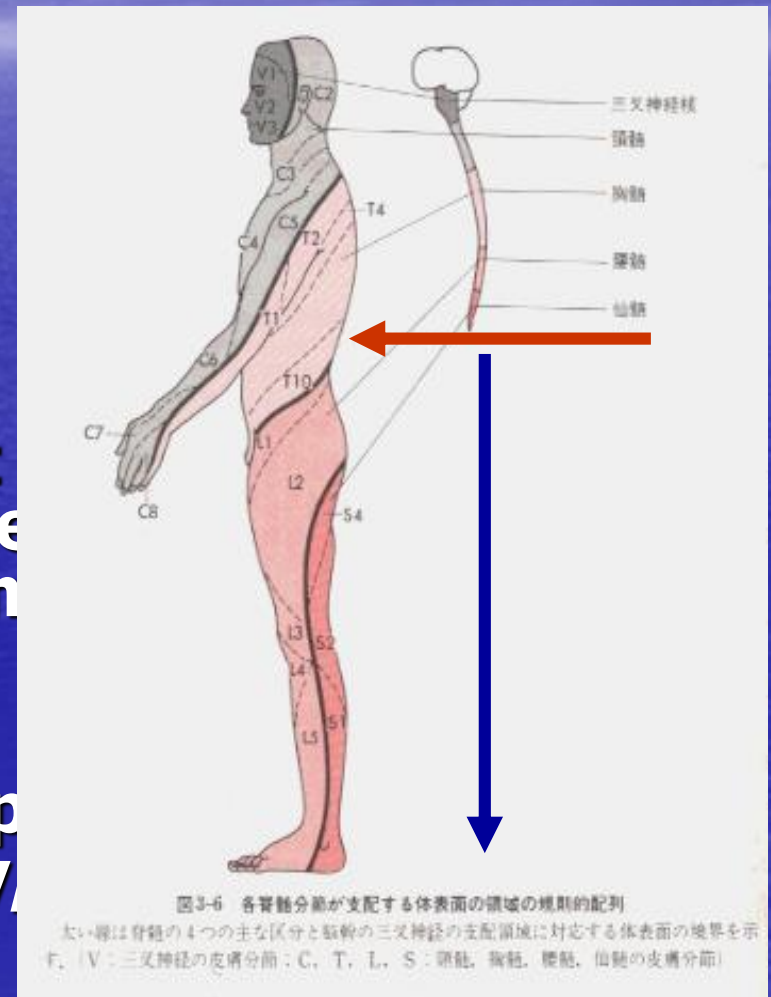
# Morphine

- Clearly produces analgesia by a spinal mechanism of action and is considered the “gold-standard” for intrathecal administered opiates. Morphine is hydrophilic and highly ionized.
- Morphine was the first opiate drug to receive FDA approval for intrathecal and epidural use.



# And what about other opiates ?

- Fentanyl, Sufentanil and Alfentanil although widely used for epidural administration does not confer any clinical benefit over the intravenous route, because the analgesic effect is mediated mainly by uptake from epidural space to plasma and redistribution to brain.
- Beside, being lipophilic, all these drugs do not spread up toward the cranial extremity, limiting their clinical use



# And now Israel.....

- In 1979, **Behar et al**, in Jerusalem, Israel reported (Lancet) the injection of morphine in the epidural space in patients suffering from cancer pain and acute postoperative pain.
- In the same year Wang, reported the intrathecal injection of morphine in patients suffering from cancer pain.

*Behar M, Magora F, Olshwang D, Davidson JT. Epidural morphine in treatment of pain. Lancet 1979, 527-529*

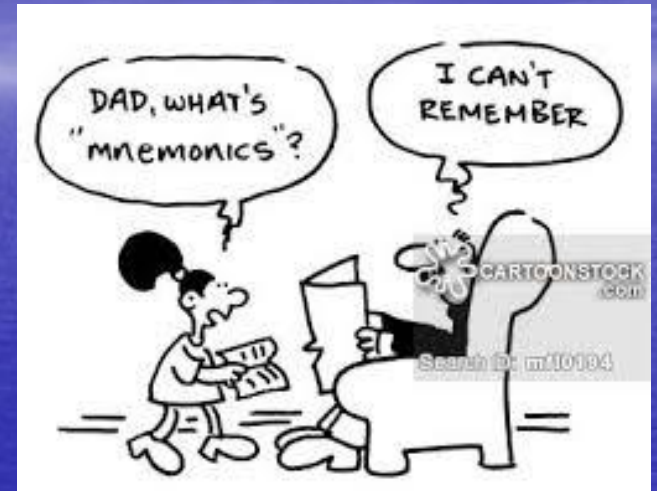
*Wang, J.K., Nauss, L.E., and Thomas, J.E.: Pain relief by intrathecally applied morphine in man. Anesthesiology, 50:149, 1979*



# The last twenty years

- **1980- Bromage reported the use of epidural opiates for postoperative pain,**
- **1981- Pasqualucci, et. al used intrathecal morphine for myocardial infarction pain.**
- **1980- Scott et al used intrathecal morphine for labor pain.**
- **1988- Epidural PCA with Morphine was described by Sjostrom et al.**

# End of the story ?!



**Da, dar pentru cei cu  
memoria ceva slabă, iată  
doar o recapitulare.....**



# The main data of the 19<sup>th</sup> century

*F. SETURNER-  
1803- isolates  
Morphine*

*C V PRAVAZ-  
1850 first syringe  
and*

*A. WOOD- 1855-  
the fist needle*

*C KOLLER-  
1884- discovers  
cocaine and J  
CORNING uses  
local anesthetics for  
epidural analgesia  
in 1885*

*H QUINCKE- 1890  
first dural puncture*

*A. BIER- 1898- first  
spinal with cocaine*

# Complementary data from the **20<sup>th</sup>** century

*N. RACOVICEANU-  
PITESTI- 1900- first spinal  
with morphine*

**TUOHY 1944-**  
the first epidural  
needle

*SJOSTROM- 1988-*  
*the first PCA epidural*

**KATAWATE-1901-** first  
combined morphine-local  
anesthetic for spinal

**BEHAR-1979-**  
first report on  
epidural  
morphine

**T. IONESCO**  
**1919-first**  
**textbook on**  
**spinal**  
**anesthesia**

**N. MIRCEA-**  
**1982-spinal**  
**pethidine**



Germany, Austria, England, Romania



# Conclusions

- **One hundred years ago , pioneers in anesthesia, surgeons by profession, discovered the advantages of regional analgesia, in comparison to the pre-modern techniques of general anesthesia.**
- **Today various opiates are used as single drugs for spinal and epidural postoperative analgesia, either by continuous infusions or patient-controlled analgesia (PCEA).**



- **During the last 100 years two countries had a significant contribution to the epidural and intrathecal use of opiates : Romania and Israel.**
- **This is not a pure coincidence that the authors of this essay were both born in Romania and continued their professional carieer to Israel.**





**Racoviceanu-Pitesti**  
**Nicolae Mircea**

**M. Behar**





Dear Past,  
Thanks for all the lessons.  
Dear Future,  
I'm ready...



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# Oare știți povestea cu cei doi cocoși, unul tânăr și altul mai bătrân?!





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