UREMIA

From where to whence

13th Congress of BANTAO

Sarajevo, 7 October 2017

Garabed Eknoyan, MD

Renal Section, Department of Medicine
Baylor College of Medicine
Houston, TX

Content of Presentation

- Origins of: UREA
- Emergence & use of: UREMIA
- Paradigm shifts in the meaning of LIFE

SUMMARY: **A Historical Reappraisal of What Happened to UREMIA**

A Framework of the Evolution of Medical Knowledge

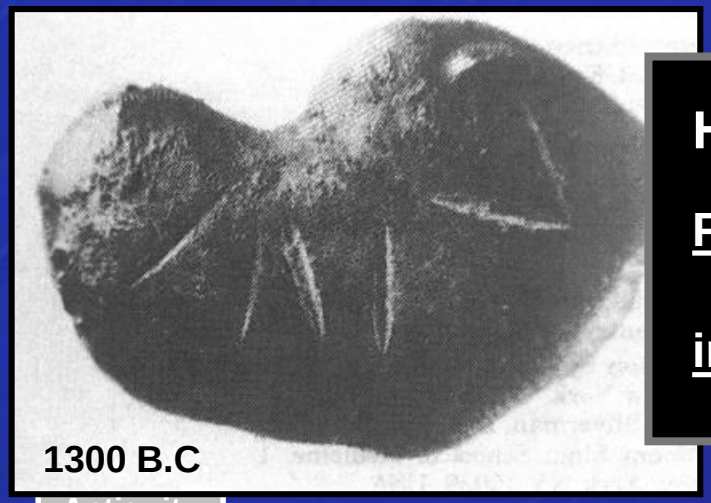
External: Signs, Symptoms — **Disease** — **Internal**: *Organs, Clinical course*

← *Clinical* — **Research** — *Basic* →

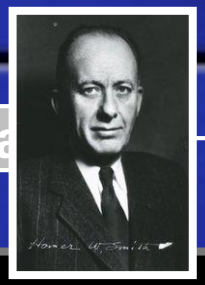
- **Early Antiquity**
- **Greece Rome**
- **Renaissance** — *Anatomy*
- **Scientific Revolution** — *Pathology Physiology*
- **Enlightenment Age of Reason** — *Chemistry Bacteriology*
- **19th Century** — *Embryology*
- 20th Century — *Genetics*

wherein the kidney …

External: Signs, Symptoms — **Disea** — **Inte** *Organs, Cl*



Antiquity



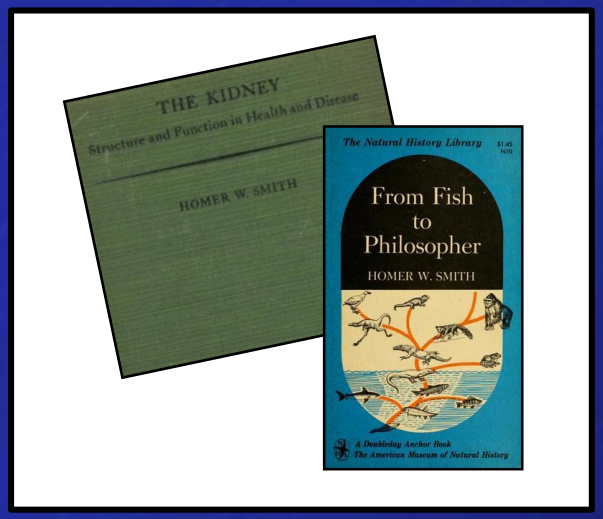
Homer W. Smith (1895-1962)

From Fish to Philosopher

The story of our

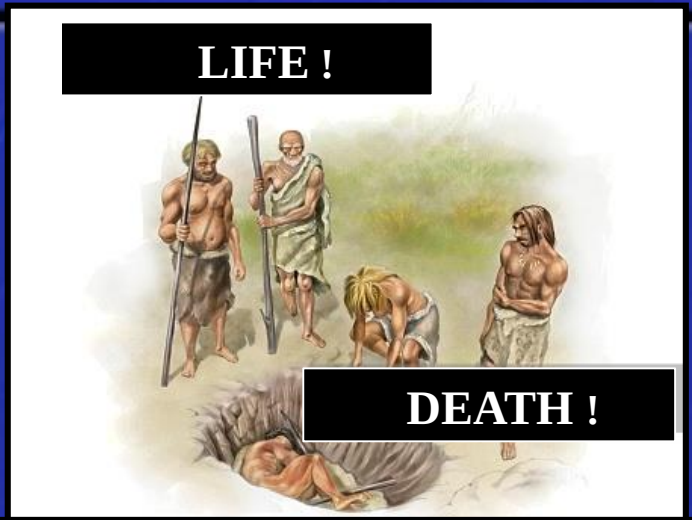
internal environment 1953

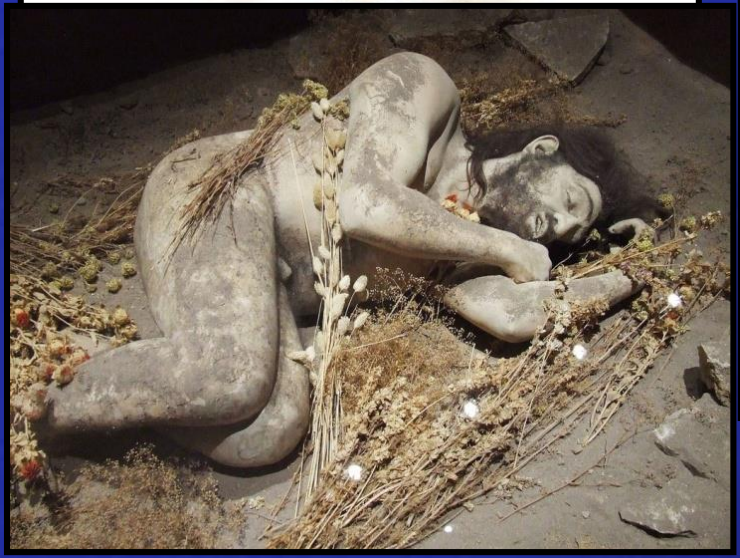
21st Century

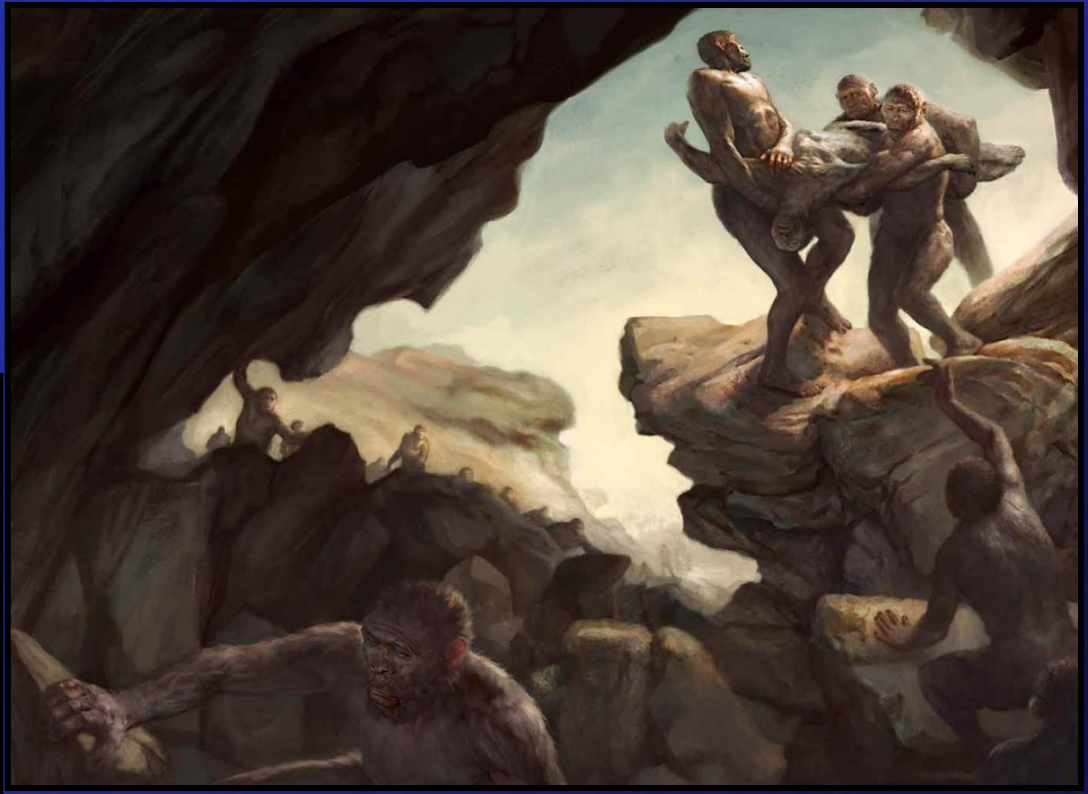


The Kidney: Structure and Function in Health and Disease 1951

Origins of medicine: LIFE/DEATH







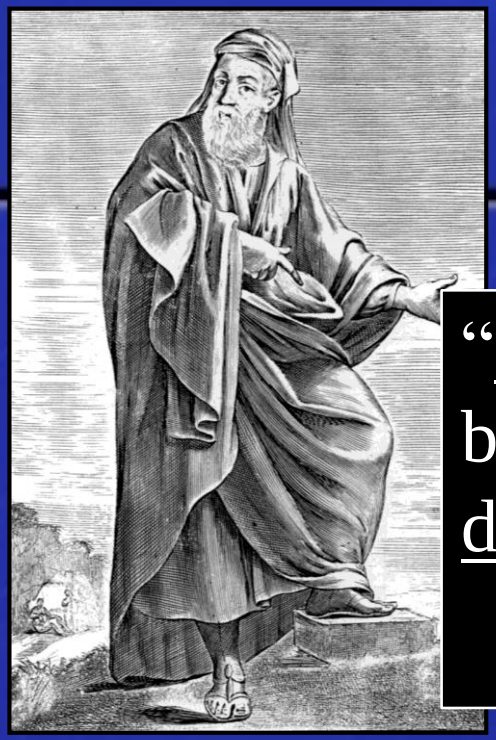
HEAT & MOVEMENT

Hypnos and Thanatos (half-brothers)

John Williams Waterhouse 1874

The "Vital" Heat

BIOLOGY



"Sleep comes about when the heat of the blood is cooled to the proper degree, death when it becomes cold altogether."

Empedocles (490-430 B.C.)

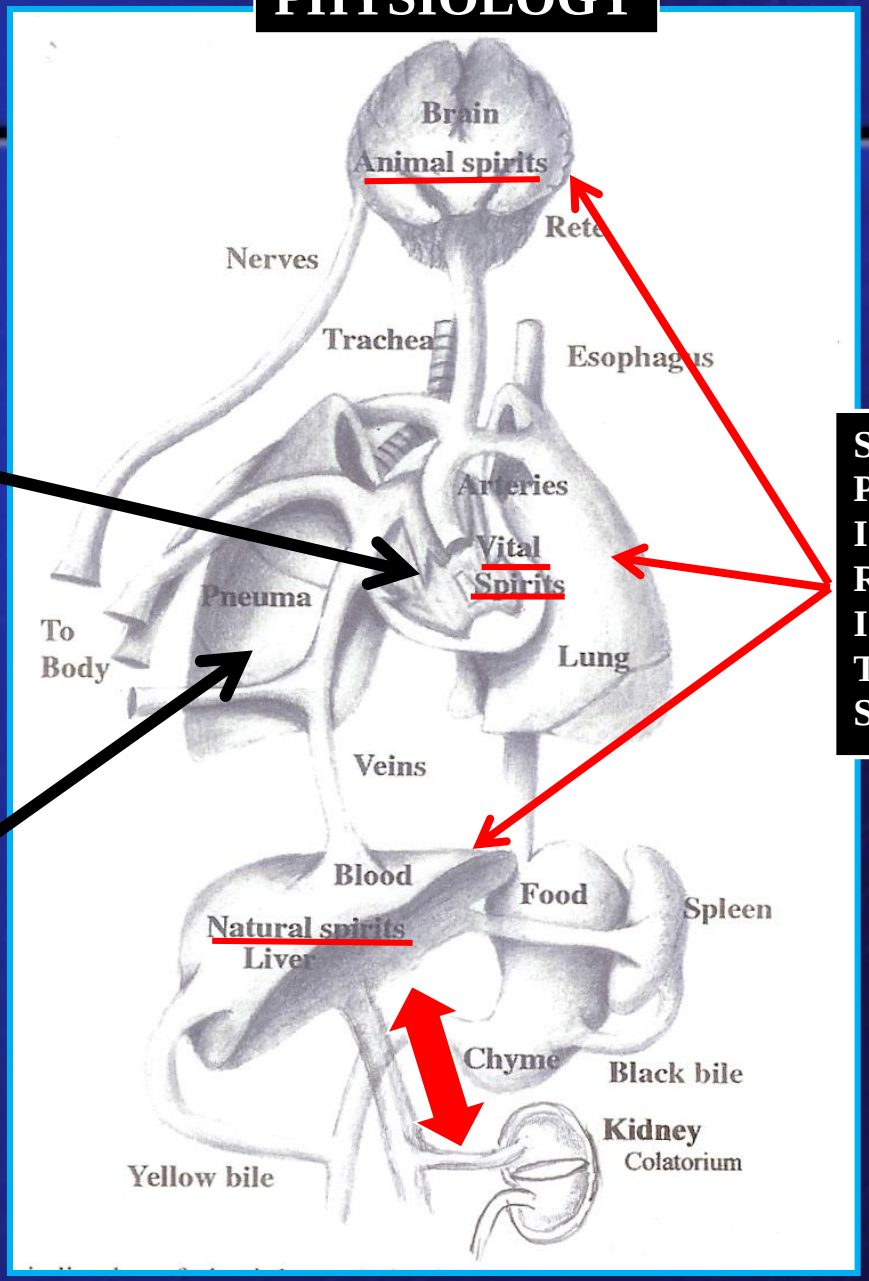
"Sleep is a temporary overpowering of the inner heat by other factors in the body, death its final extinction."

Aristotle (384-322 B.C.)

Galen (120-200 A.D.)

'VITAL HEAT'
caladium innatum

PHYSIOLOGY



SPIRITS

Quentyn Matsys, copy 17th century
***Louvre Museum**, Paris*

Paracelsus

(1493-1541)

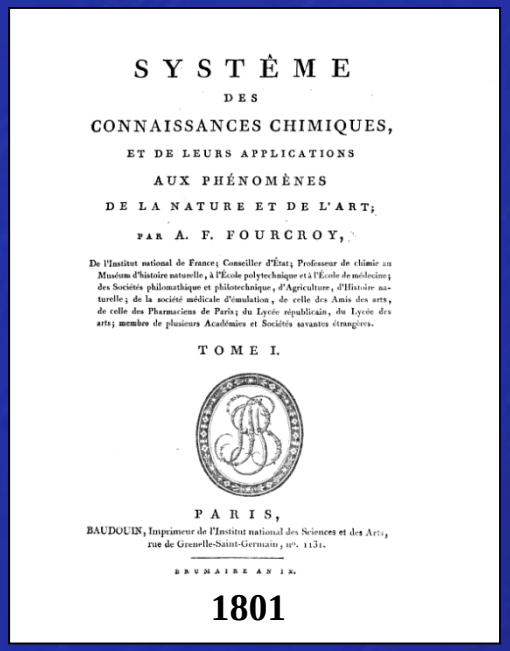
1. Challenged scholasticism
2. Alchemy ⟶ Chemistry
3. **Urine** and (Blood) analysis

CHEMISTRY

1. **Mercury** *smoke*
2. **Sulphur** *combustible*
3. **Salt** *residue*

NDT 1996;11:1388-1394

Antoine **FOURCROY** (1755-1809)



SYSTÈME
DES
CONNAISSANCES CHIMIQUES,
ET DE LEURS APPLICATIONS
AUX PHÉNOMÈNES
DE LA NATURE ET DE L'ART;
PAR A. F. FOURCROY,

De l'Institut national de France; Conseiller d'État; Professeur de chimie au Muséum d'histoire naturelle, à l'École polytechnique et à l'École de médecine; des Sociétés philomathique et philotechnique, d'Agriculture, d'Histoire naturelle; de la société médicale d'émulation, de celle des Amis des arts, de celle des Pharmaciens de Paris; du Lycée républicain, du Lycée des arts; membre de plusieurs Académies et Sociétés savantes étrangères.

TOME I.

PARIS,
BAUDOUIN, Imprimeur de l'Institut national des Sciences et des Arts, rue de Grenelle-Saint-Germain, n°. 1131.

BRUMAIRE AN IX.

1801

"This liquid … has become, in the hands of chemists, a source of important discoveries, and is an object in the history of which we find the most valuable notion which the study of it affords the physiologist."

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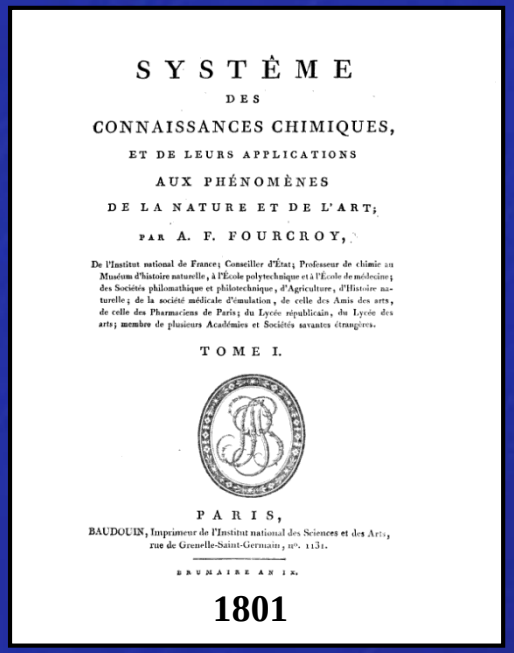

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Enter: **Animal "Oeconomy"**

"oeconomia animalis"

OBSERVATIONS

ON

CERTAIN PARTS

OF THE

ANIMAL OECONOMY.

BY JOHN HUNTER.

SECOND EDITION.

LONDON;

PRINTED AND SOLD AT Nº 13, CASTLE-STREET, LEICESTER-SQUARE;

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MDCCXCII.

Medicina Gymnastica:

OR, A

TREATISE

Concerning the

POWER of EXERCISE,

With Respect to the

ANIMAL OECONOMY;

AND

The Great Necessity of it,

IN THE

Cure of Several Distempers.

By *FRANCIS FULLER*, M.A.

The FOURTH EDITION.

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Printed for ROBERT KNAPLOCK, at the *Bishop's-Head* in St. *Paul's* Church-Yard. 1711.

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Describing the

Animal Oeconomy,

AND A

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Of many

DISTEMPERS

Incident to

HUMAN BODIES.

Illustrated with above Fourscore Figures, drawn after the Life.

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ON THE

ANIMAL OECONOMY,

AND ON THE

CAUSES AND CURE OF DISEASES.

By JOHN GARDINER, M.D.

PRESIDENT OF THE ROYAL COLLEGE OF PHYSICIANS, AND FELLOW OF THE ROYAL SOCIETY OF EDINBURGH.

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INTO THE

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1794.

A

COURSE

OF

Anatomico-Physiological

LECTURES

ON THE

HUMAN STRUCTURE

AND

ANIMAL OECONOMY;

Interspersed with

Various Critical NOTES, extracted from Memoirs, Transactions of Learned SOCIETIES, &c. and Pathological Observations deduced from the Dissection of morbid Bodies.

INCLUDING

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PARTICULARLY

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Illustrated with

An HISTORICAL COMPENDIUM of the Rise, Progress, and Discoveries, which have been made in the ANIMAL OECONOMY, gradually traced to the present Time.

To which are prefixed,

TWO ESSAYS on the ART of Dissecting, Injecting and Making ANATOMICAL PREPARATIONS.

VOL. I.

Omne tulit punctum, qui miscuit utile dulci. HOR.

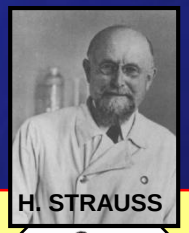
By CHARLES NICHOLAS JENTY, M.A.

Professor of ANATOMY and SURGERY.

LONDON,

Printed for JAMES PHINN and JAMES FLETCHER, at the Oxford Theatre in Paternoster Row. MDCCLXXII.

Enter: UREA



Early Antiquity

Greece Rome

Renaissance

Scientific Revolution

Enlightenment Age of Reason

19th Century

20th Century

Anatomy

Physiology
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Embryology

Genetics

LIFE
Force
Vitality
Humor
Soul
Juices
Life Spark

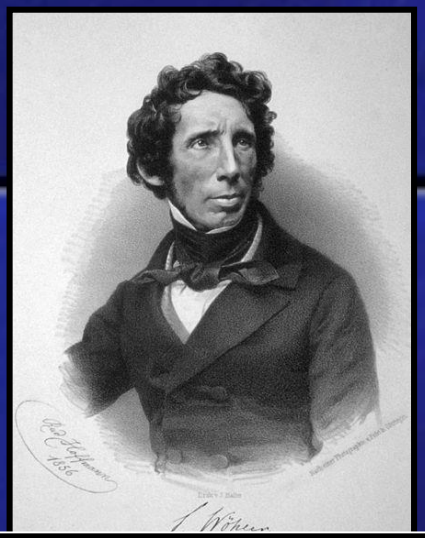
VITAL SPIRIT

Discovery of UREA in URINE

- **1664** ***J. B. van Helmont*** "a natural ***salt*** in the urine"
- **1732** ***H. Boerhaave*** "saponaceous ***salt*** that ***tastes*** different from sea salt"
- **1773** ***H. Rouelle*** high nitrogen content, ***octahedral crystals*** octahedral rather than cubic crystals of sea salt
- **1785** ***C. Berthollet*** urea source of ammonia in urine
- **1798** ***W. Cruickshank*** crystallizes with nitric acid in *diabetic* urine
- **1799-1808** **A. Fourcroy & N. Vauquelin** estimated nitrogen content in crystals, coined **"*URÉE*", *Urea***

1827 *“Annus mirabilis”*

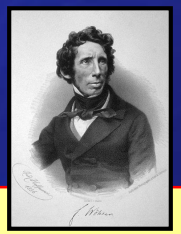
Berlin, 22nd February 1828



Friedrich **Wöhl**er (1800-1882)

“I write already again because I cannot, so to say, hold my chemical water and must tell you that ***I can make urea without the help of a kidney or even an animal, neither man nor dog. ”***

Enter: UREA



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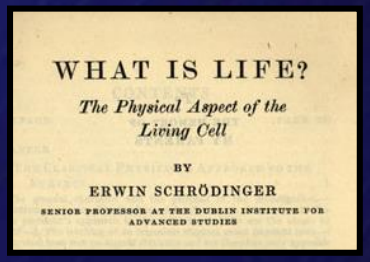

WHAT IS LIFE?

The Physical Aspect of the Living Cell

BY

ERWIN SCHRÖDINGER

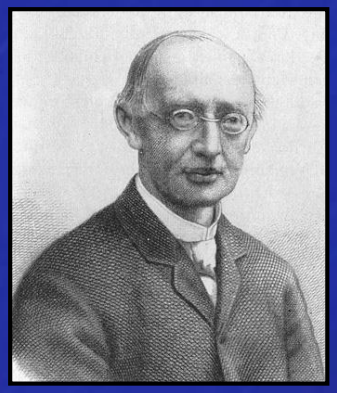
SENIOR PROFESSOR AT THE DUBLIN INSTITUTE FOR ADVANCED STUDIES

1827 *"Annus mirabilis"* **

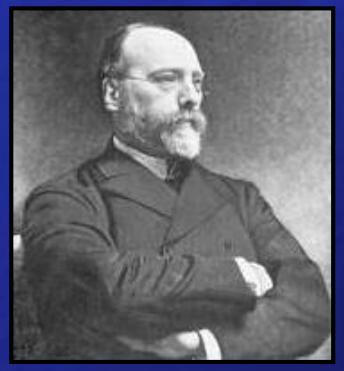
- 1810s ***J. Bostock*** Blood urea elevated in some of Bright's cases
- 1821 ***J. Provost & J Dumas*** Extra-renal origin of urea, BUN increases after nephrectomy
- **1827 *F. Wöhler*** Urea synthesis
- **1827 *R. Bright*** Bright's Disease
- 1829 ***R. Christison*** Blood urea increased in kidney diseases
- **1847 P. Piorry & G. Andral "Urémie"**, Uremia

Enter: **Uremia**

Adolphe **PIORRY** 1794-1879



Friedrich **FRERRICHS** 1819-1885



Charles **BOUCHARD** 1837-1915

1847

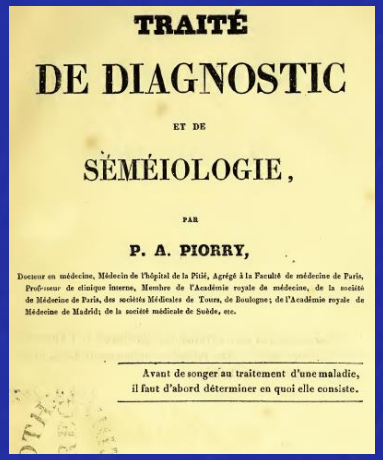
Urémie

1851

Urämische intoxication

1894

Ptomaines



TRAITÉ

DE DIAGNOSTIC

ET DE

SÉMÉIOLOGIE,

PAR

P. A. PIORRY,

Docteur en médecine, Médecin de l'hôpital de la Pitié, Agrégé à la Faculté de médecine de Paris, Professeur de clinique interne, Membre de l'Académie royale de médecine, de la société de Médecine de Paris, des sociétés Médicales de Tours, de Boulogne; de l'Académie royale de Médecine de Madrid; de la société médicale de Suède, etc.

Avant de songer au traitement d'une maladie, il faut d'abord déterminer en quoi elle consiste.

Die

Bright'sche Nierenkrankheit

und deren

Behandlung.

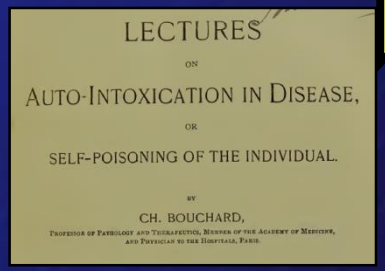
Eine

Monographie

von

Dr. Friedr. Theod. Frerichs,

ordentlich. Professor der Medicin und Vorstand der medicinischen Klinik in Kiel.



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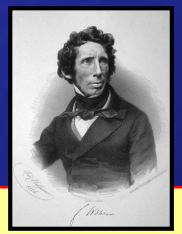

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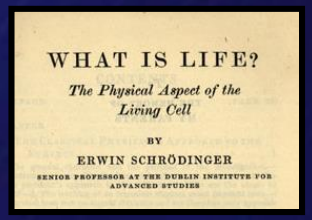
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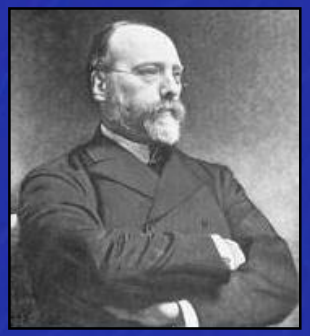
State of the Art: Functional Tests of CKD

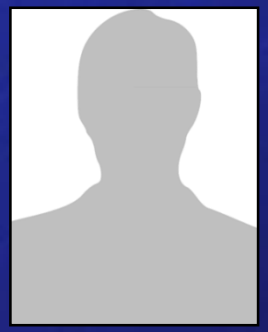


Charles **BOUCHARD** 1837-1915

Sandor **KORANYI** 1866-1944

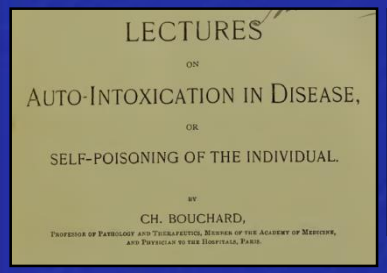
Charles **ACHARD** 1860-1944

Leonard **ROWNTREE** 1883-1959



John **GERAGHTY** 1876-1924

1894 — **Urine Toxicity**



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1896 — **FPD Test**

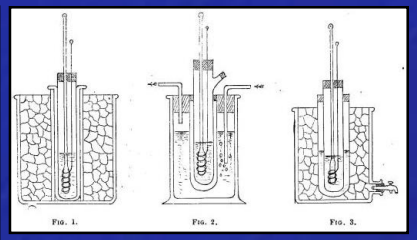
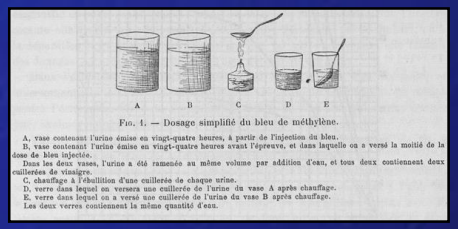


Fig. 1. Fig. 2. Fig. 3.

1897-1900 — **Methylene Blue (phloridzin)**

6141

*6141.— Flacon de comprimés de trioxyméthylène.

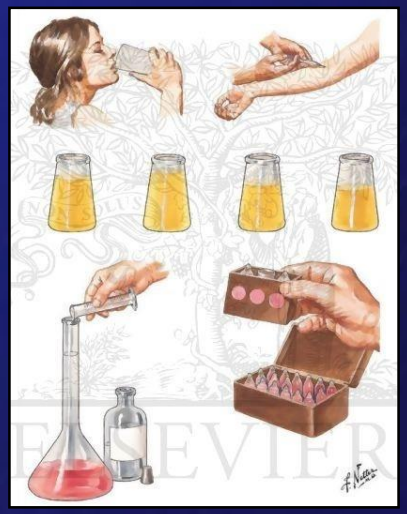


A B C D E

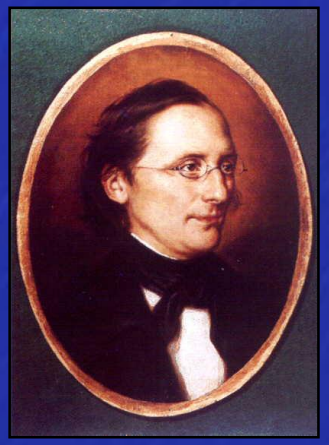
Fig. 1. — Dosage simplifié du bleu de méthylène.

A, vase contenant l'urine émise en vingt-quatre heures, à partir de l'injection du bleu.
B, vase contenant l'urine émise en vingt-quatre heures avant l'épreuve, et dans laquelle on a versé la moitié de la dose de bleu injectée.
Dans les deux vases, l'urine a été ramenée au même volume par addition d'eau, et tous deux contiennent deux cuillerées de vinaigre.
C, chauffage à l'ébullition d'une cuillerée de chaque urine.
D, verre dans lequel on versera une cuillerée de l'urine du vase A après chauffage.
E, verre dans lequel on a versé une cuillerée de l'urine du vase B après chauffage.
Les deux verres contiennent la même quantité d'eau.

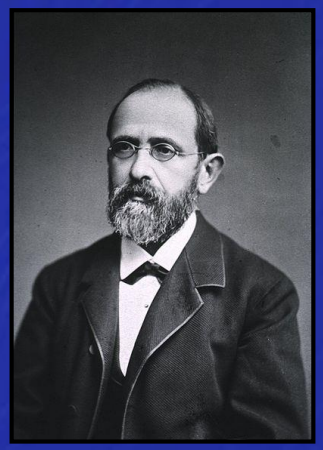
1910 — **PSP Test**



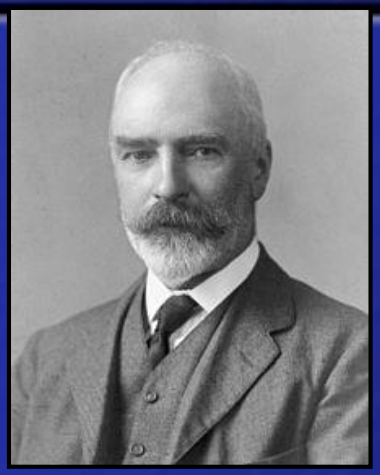
Kidney Function 1842-1942



Carl **LUDWIG** 1816-1895



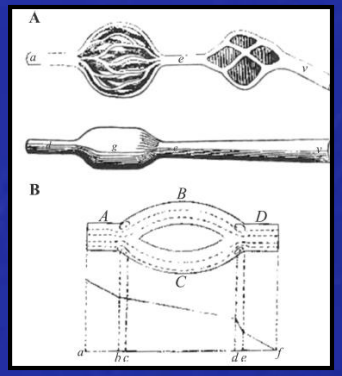
Rudolph **HEIDENHAIN** 1834-1897

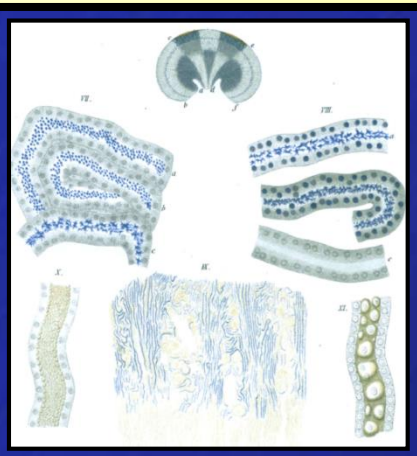


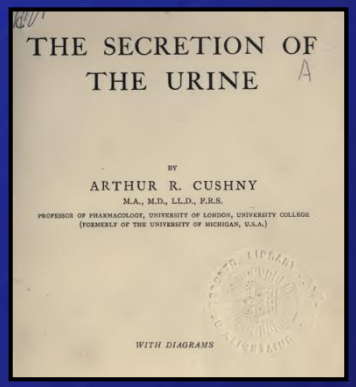
Arthur **CUSHNY** 1866-1926

HOMER **SMITH** 1895-1962

1842-1917 **1917-1926** **1926-1951**







THE SECRETION OF THE URINE

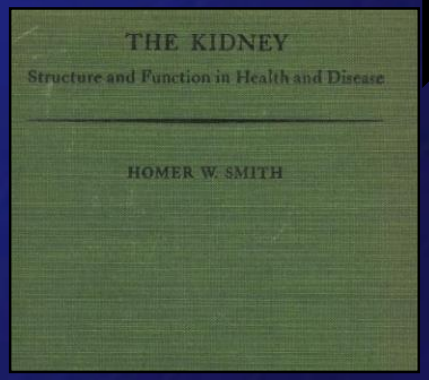
BY

ARTHUR R. CUSHNY

M.A., M.D., LL.D., F.R.S.

PROFESSOR OF PHARMACOLOGY, UNIVERSITY OF LONDON, UNIVERSITY COLLEGE (FORMERLY OF THE UNIVERSITY OF MICHIGAN, U.S.A.)

WITH DIAGRAMS



THE KIDNEY

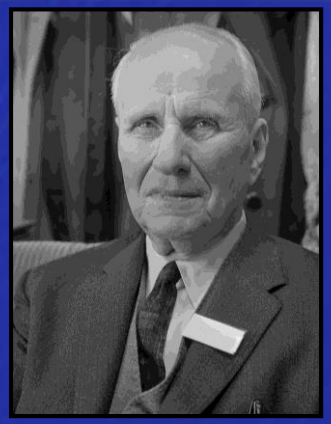
Structure and Function in Health and Disease

HOMER W. SMITH

Adv Physiol Educ 2014;38:286-295

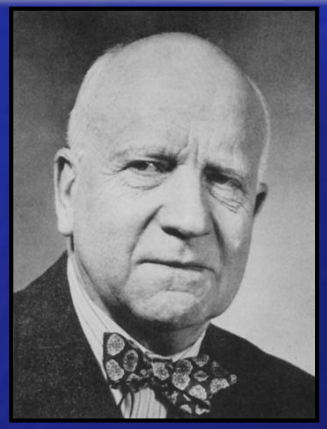
State of the Art: Functional Tests of CKD

Léon **AMBARD** 1876-1962



Franklin **McLEAN** 1888-1968

Thomas **ADDIS** 1881-1949



Donald **Van SLYKE** 1883-1971

1910-12 **1915-17** **1923-8** **1926-8**

$$\frac{Ur}{\sqrt{D \times \frac{70}{Wt} \times \sqrt{\frac{C}{25}}}} = K \text{ (constant).}$$

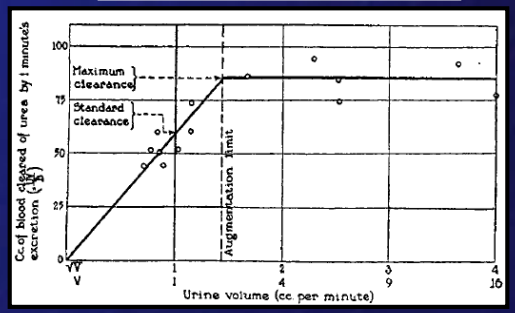
Ur = gm. of urea per liter of blood.
D = gm. of urea excreted per 24 hours.
Wt = weight of individual in kilos.
C = gm. of urea per liter of urine.

$$\text{Index of urea excretion (I)} = \frac{D\sqrt{C} \times 8.96}{Wt. \times Ur.^2}$$

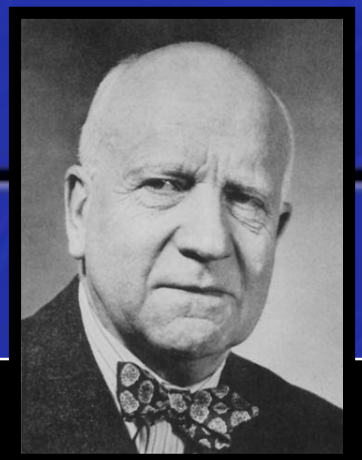
D = gm. of urea excreted per 24 hours.
C = " " " per liter of urine.
Ur. = " " " " " " blood.
Wt. = body weight of individual, in kilos.

UV/P

Clearance



Chem Rev 1940:26:105-127



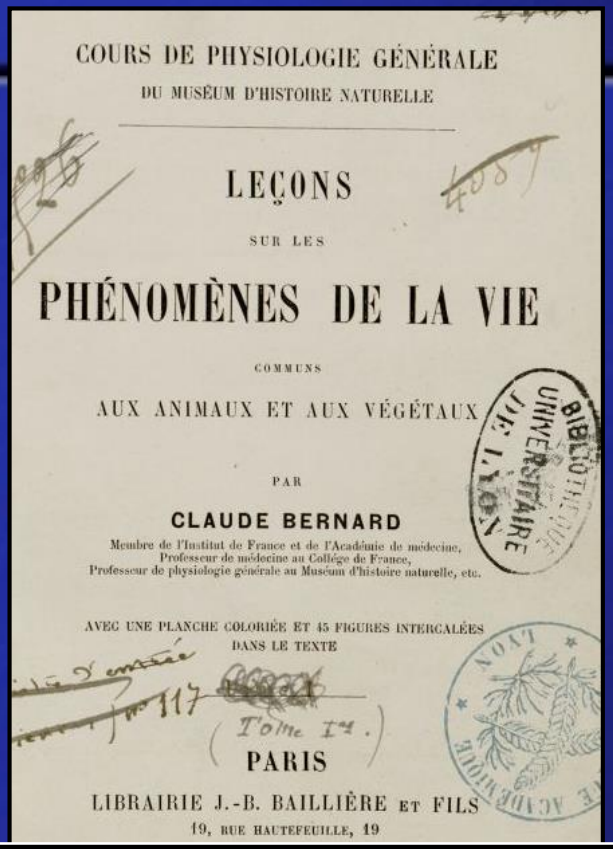
“Milieu intérieur”, redux

“Our cells are bathed in a fluid … have maintained a fastidious preference for a surrounding medium of constant and definite composition; and if they are outraged by brusque changes in this medium they refuse to perform their aliquots parts of the body’s functions.”

Donald D. Van Slyke

Chem Rev1940;26:105-127
***From fish to philosopher**, the story of our internal environment, 1953*

Claude BERNARD (1813-1878)



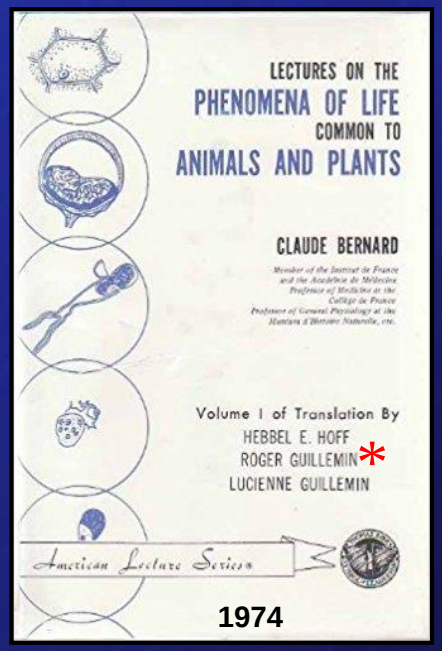
COURS DE PHYSIOLOGIE GÉNÉRALE
DU MUSÉUM D'HISTOIRE NATURELLE

LEÇONS
SUR LES
PHÉNOMÈNES DE LA VIE
COMMUNS
AUX ANIMAUX ET AUX VÉGÉTAUX

PAR
CLAUDE BERNARD
Membre de l'Institut de France et de l'Académie de médecine,
Professeur de médecine au Collége de France,
Professeur de physiologie générale au Muséum d'histoire naturelle, etc.

AVEC UNE PLANCHE COLORIÉE ET 45 FIGURES INTERCALÉES
DANS LE TEXTE

(Tome Ier.)
PARIS
LIBRAIRIE J.-B. BAILLIÈRE ET FILS
19, RUE HAUTEFEUILLE, 19



LECTURES ON THE
PHENOMENA OF LIFE
COMMON TO
ANIMALS AND PLANTS

CLAUDE BERNARD

Volume I of Translation By
HEBBEL E. HOFF
ROGER GUILLEMIN*
LUCIENNE GUILLEMIN

American Lecture Series

1974

"The stability of the internal environment (*milieu intérieur*) is the condition for the free and independent life"

Walter B. CANNON (1871-1945)

No. 5064

AMERICAN EXPEDITIONARY FORCES

Corps Expéditionnaires Américains

IDENTITY CARD

CARTE D'IDENTITÉ

Name *Nom* WALTER B. CANNON

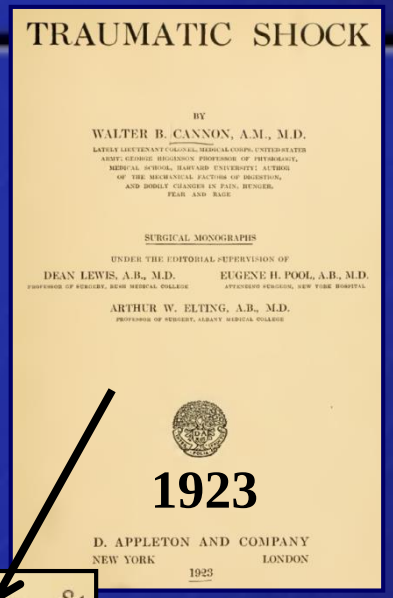
Rank *Grade* MAJOR, M.R.C.

Duty *Fonction* IN CHARGE SURGICAL RESERCH LABORATORY CENTRAL MED. DEPT. LABORATORIES

Signature of Holder *Signature du Titulaire* Walter B. Cannon

Adjutant General

Upon relief from duty with the A. E. F. the holder must turn in this Card to the C. O. at the port of embarkation.


TRAUMATIC SHOCK

BY

WALTER B. CANNON, A.M., M.D.

LATELY LIEUTENANT COLONEL, MEDICAL CORPS, UNITED STATES ARMY; GEORGE HIGGINSON PROFESSOR OF PHYSIOLOGY, MEDICAL SCHOOL, HARVARD UNIVERSITY; AUTHOR OF THE MECHANICAL FACTORS OF DIGESTION, AND BODILY CHANGES IN PAIN, HUNGER, FEAR AND RAGE

SURGICAL MONOGRAPHS

UNDER THE EDITORIAL SUPERVISION OF

DEAN LEWIS, A.B., M.D. — PROFESSOR OF SURGERY, RUSH MEDICAL COLLEGE

EUGENE H. POOL, A.B., M.D. — ATTENDING SURGEON, NEW YORK HOSPITAL

ARTHUR W. ELTING, A.B., M.D. — PROFESSOR OF SURGERY, ALBANY MEDICAL COLLEGE

1923

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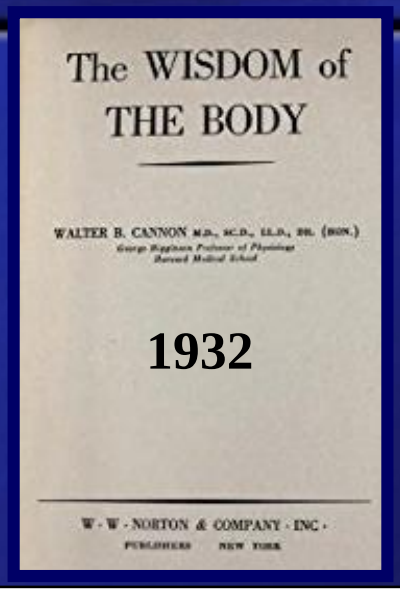
NEW YORK LONDON

1923


The WISDOM of THE BODY

WALTER B. CANNON M.D., SC.D., LL.D., DR. (HON.)

George Higginson Professor of Physiology Harvard Medical School

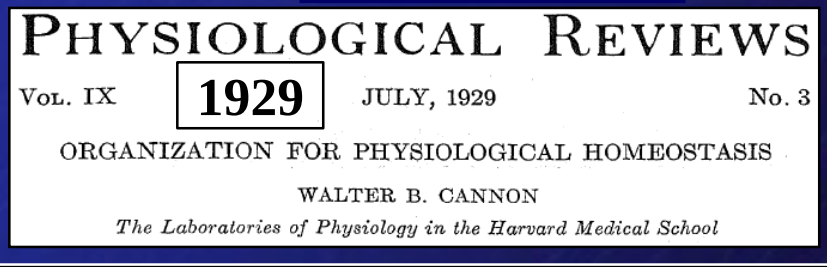
1932

W · W · NORTON & COMPANY · INC ·

PUBLISHERS NEW YORK

XI. SOME CHANGES IN BLOOD AND URINE 84

Traumatic leukocytosis, 84—The sugar content of the blood, 85—Nitrogen retention in the wounded, 86—Changes in urinary constitutents, 88.


PHYSIOLOGICAL REVIEWS

VOL. IX **1929** JULY, 1929 No. 3

ORGANIZATION FOR PHYSIOLOGICAL HOMEOSTASIS

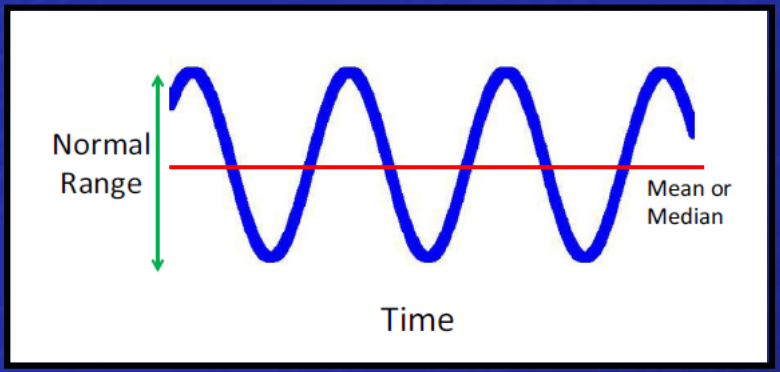
WALTER B. CANNON

The Laboratories of Physiology in the Harvard Medical School

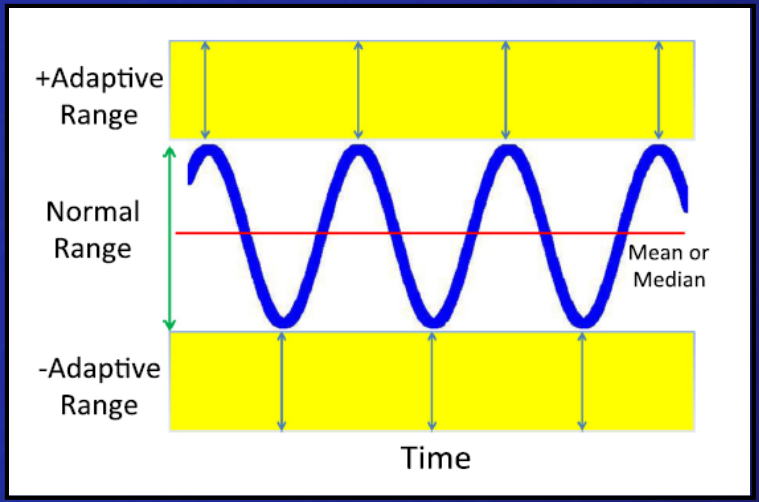
HOMEOSTASIS

"The physiological processes that regulate and maintain the steady states of the body "

Constancy of the Internal Environment

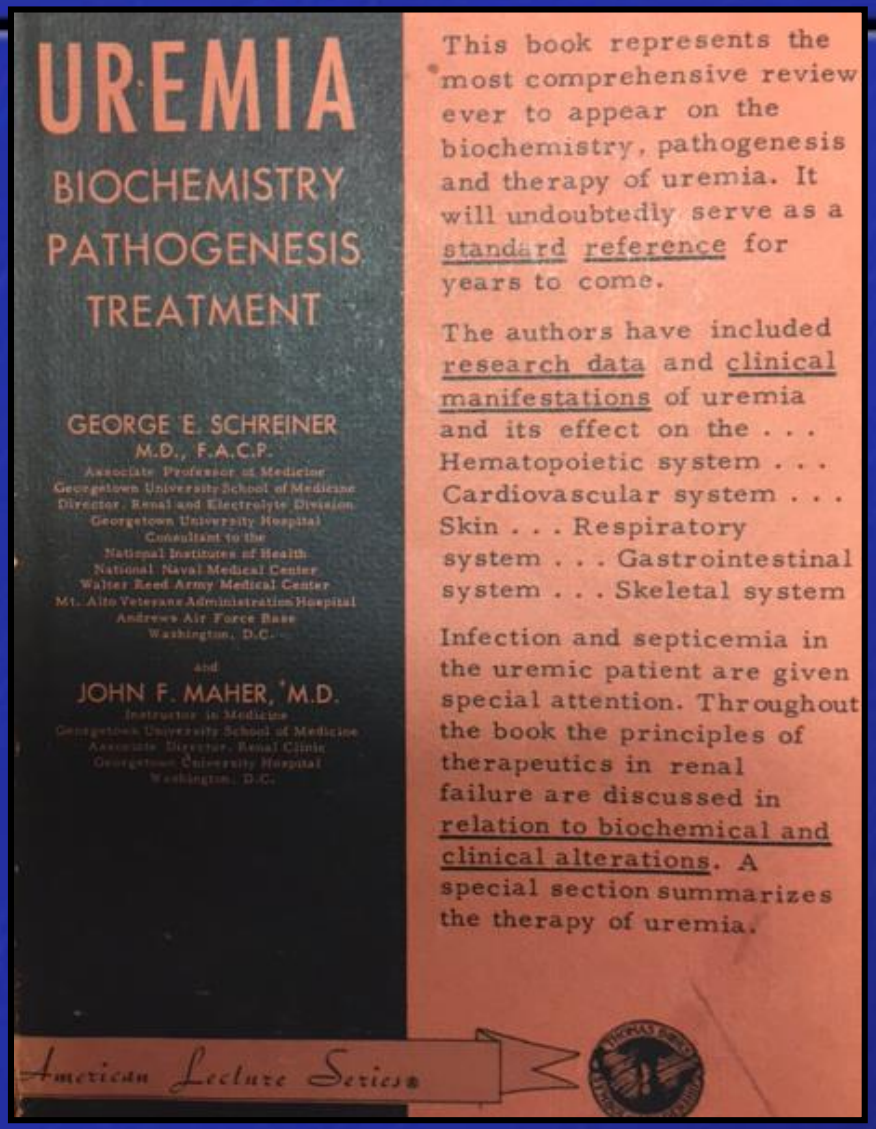


Normal



Adaptive Changes

UREMIA 1960



UREMIA

BIOCHEMISTRY
PATHOGENESIS
TREATMENT

GEORGE E. SCHREINER
M.D., F.A.C.P.
Associate Professor of Medicine
Georgetown University School of Medicine
Director, Renal and Electrolyte Division
Georgetown University Hospital
Consultant to the
National Institutes of Health
National Naval Medical Center
Walter Reed Army Medical Center
Mt. Alto Veterans Administration Hospital
Andrews Air Force Base
Washington, D.C.

and

JOHN F. MAHER, M.D.
Instructor in Medicine
Georgetown University School of Medicine
Associate Director, Renal Clinic
Georgetown University Hospital
Washington, D.C.

This book represents the most comprehensive review ever to appear on the biochemistry, pathogenesis and therapy of uremia. It will undoubtedly serve as a standard reference for years to come.

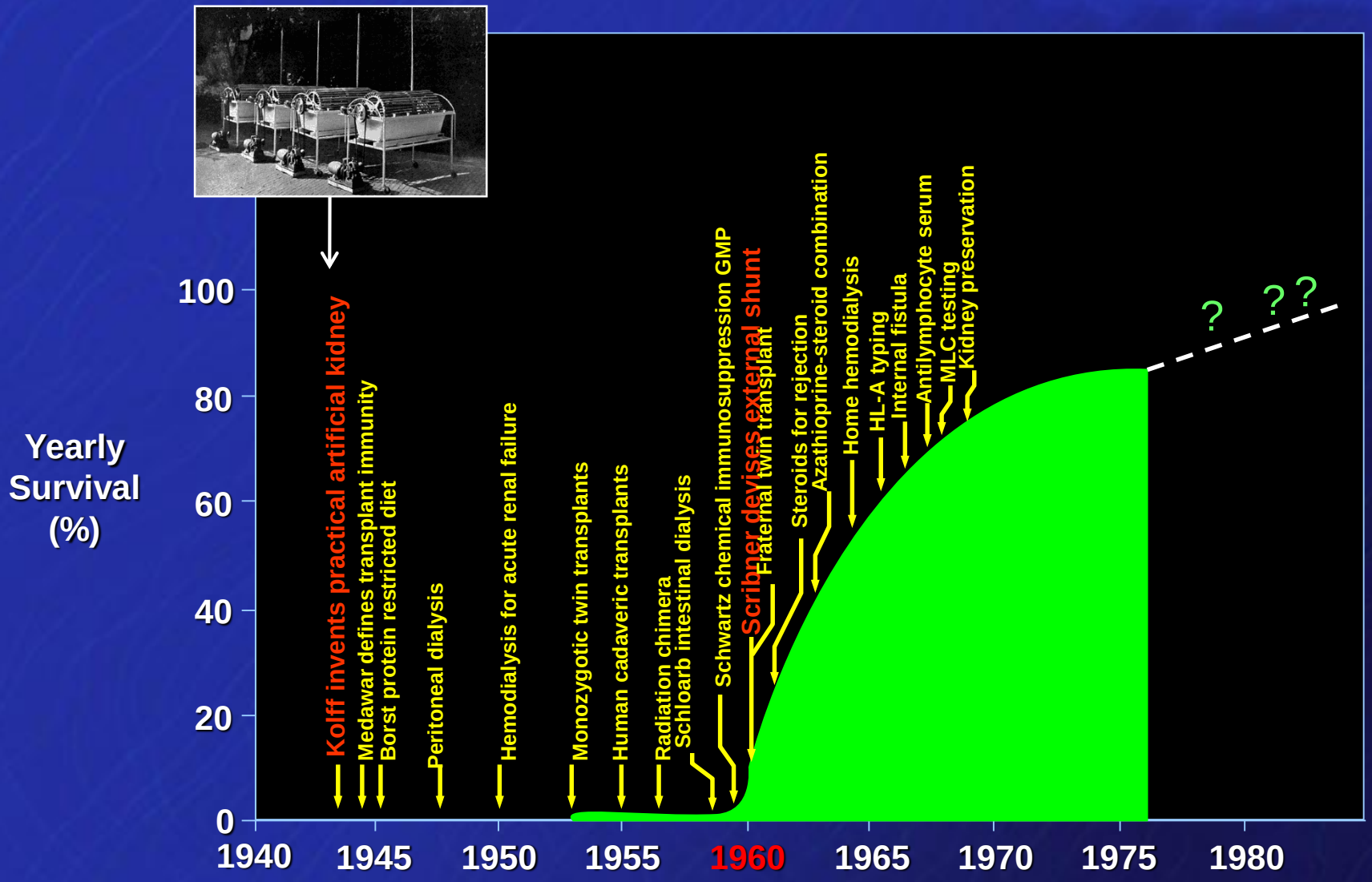
The authors have included research data and clinical manifestations of uremia and its effect on the . . . Hematopoietic system . . . Cardiovascular system . . . Skin . . . Respiratory system . . . Gastrointestinal system . . . Skeletal system

Infection and septicemia in the uremic patient are given special attention. Throughout the book the principles of therapeutics in renal failure are discussed in relation to biochemical and clinical alterations. A special section summarizes the therapy of uremia.

American Lecture Series

"A syndrome reflecting the summation of a series of altered contol and feedback mechanisms centered on the kidney that account for the altered biochemical and clinical abnormalities observed clinically."

Enter: **DIALYSIS**

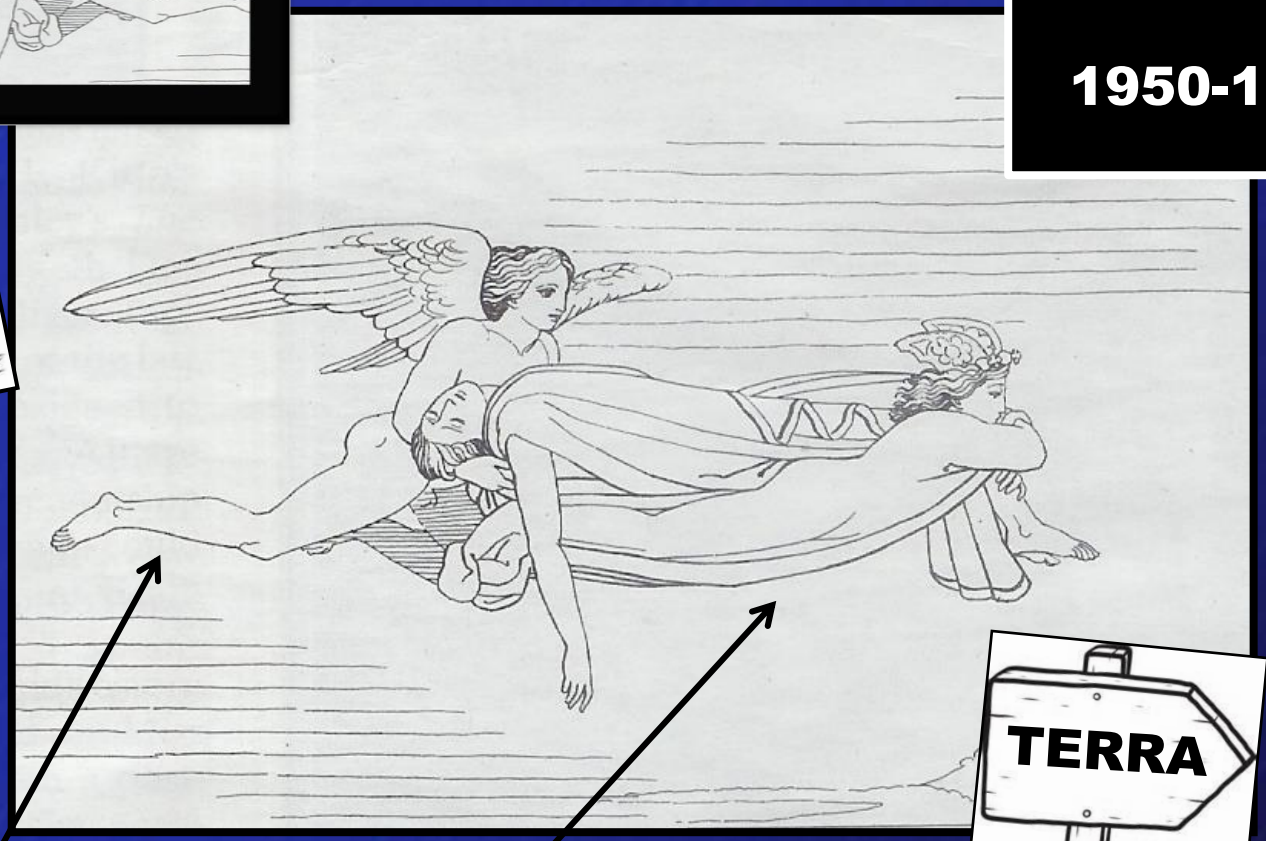


UREMIA

GREECE 500 BC

HADES

1950-1962



TERRA

HYPNOS and THANATOS

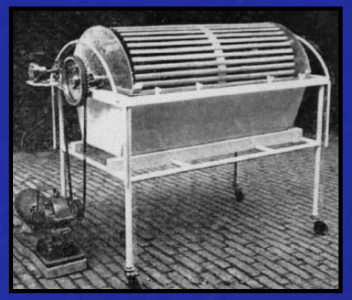
Renaissance of UREA

- **1827** *H. Dutrochet* "Osmosis"
- **1850** *T. Graham* Osmotic forces and "Dialysis"

- **1913** *J. J. Abel*

  blood by dialy

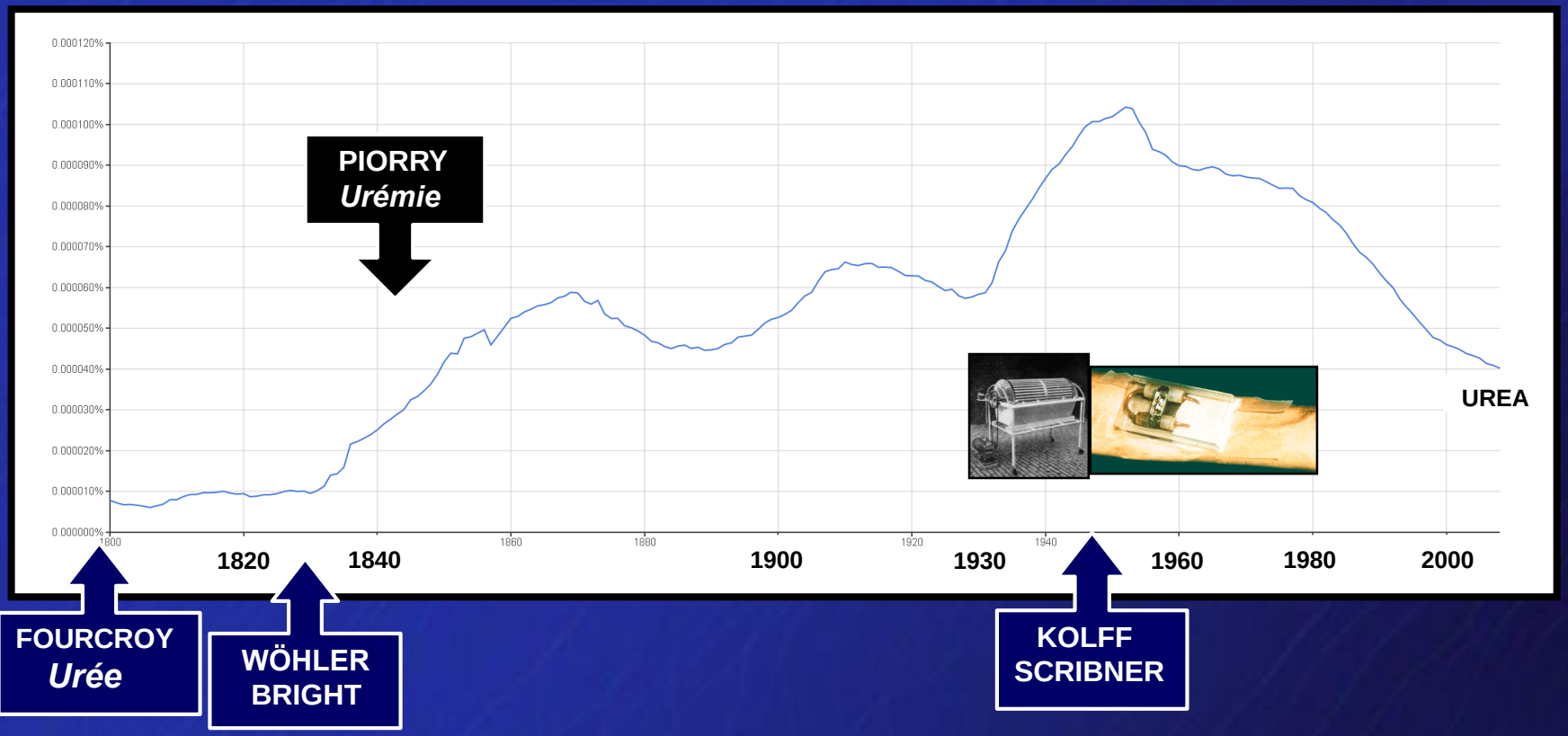
- **1940s** *W. Kolff*



UREA as marker of ADEQUACY

1. TAC_{urea}
2. URR
3. Kt/V
4. **TOXIN**

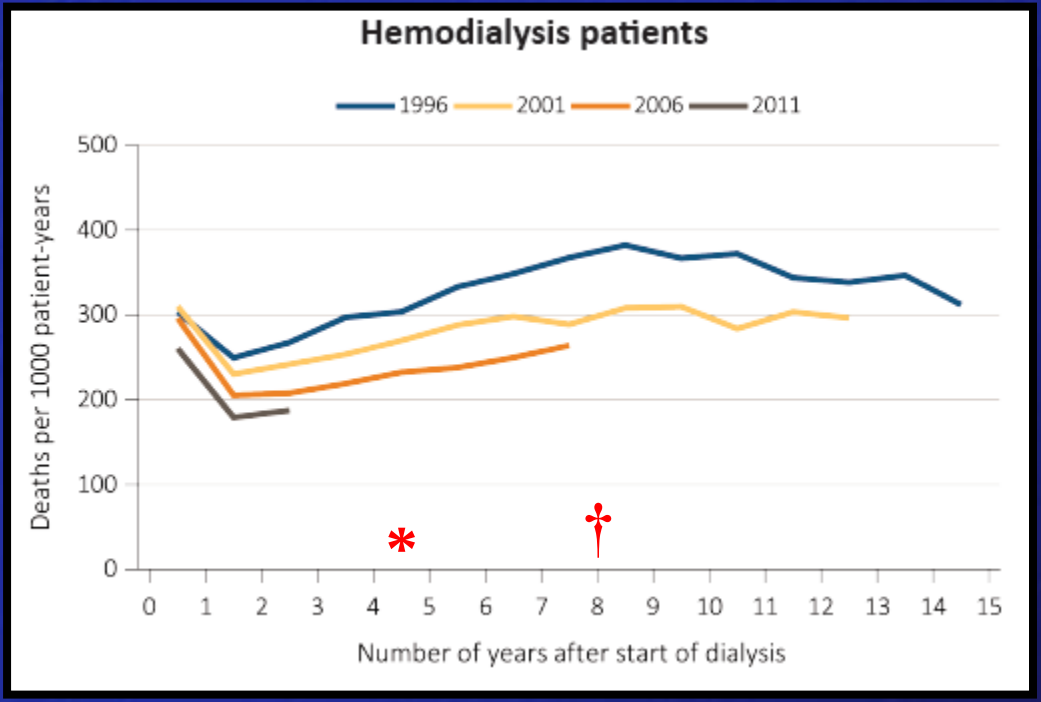
Relative frequency of the use of the word UREA



Google Books Ngram Viewer

CONCERNS

Adjusted ACM in Hemodialysis patients



* 60-64 yrs. olds *vs.* general population of **17-22 yrs**

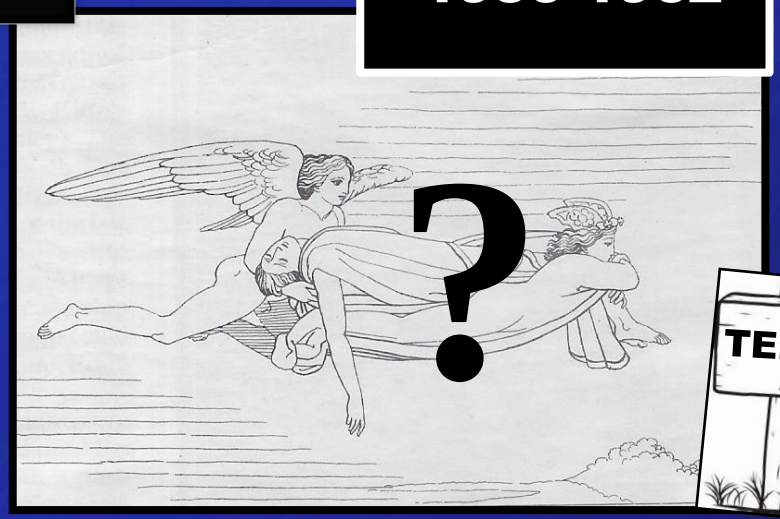
† 30-40 yrs old *vs.* general population of **30-40 yrs**

USRDS Annual Data Report-2016

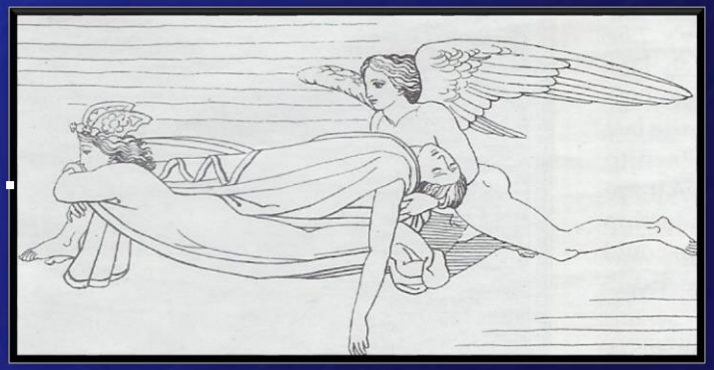
UREMIA

GREECE 500 BC

1950-1962

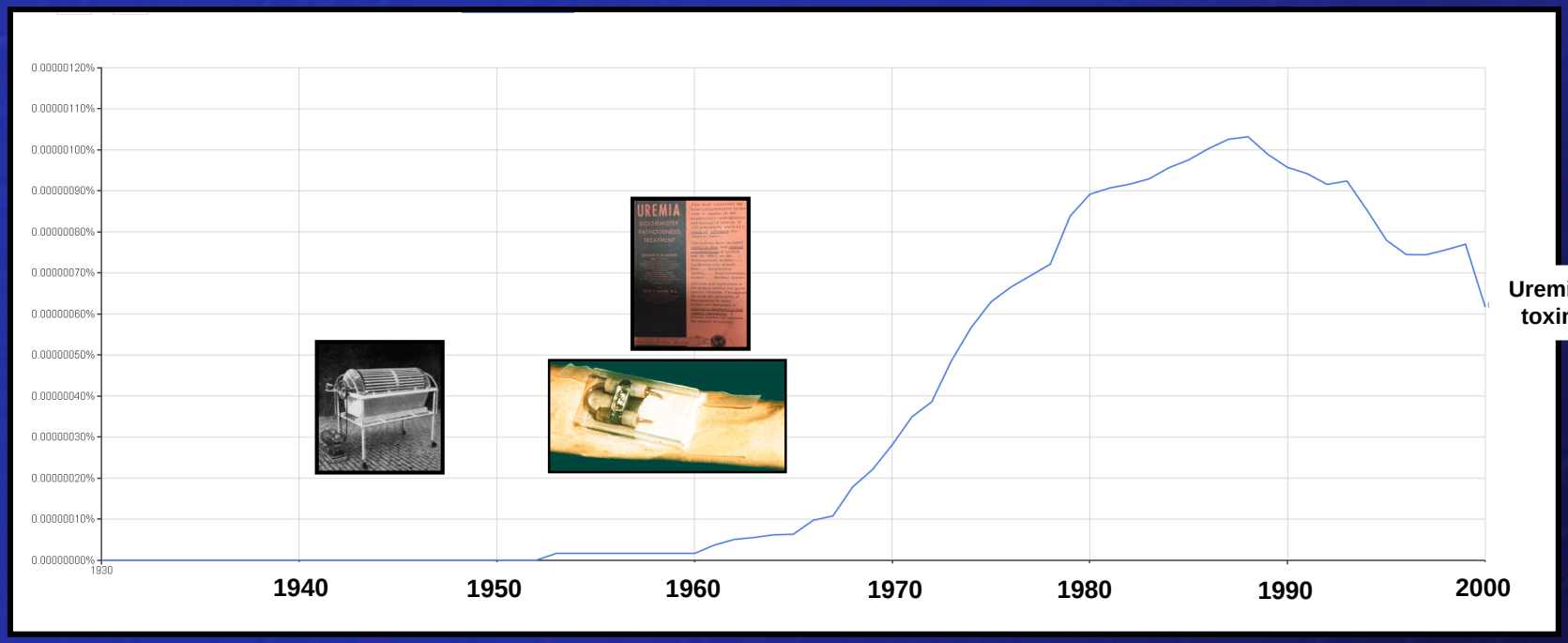


HYPNOS and THANATOS



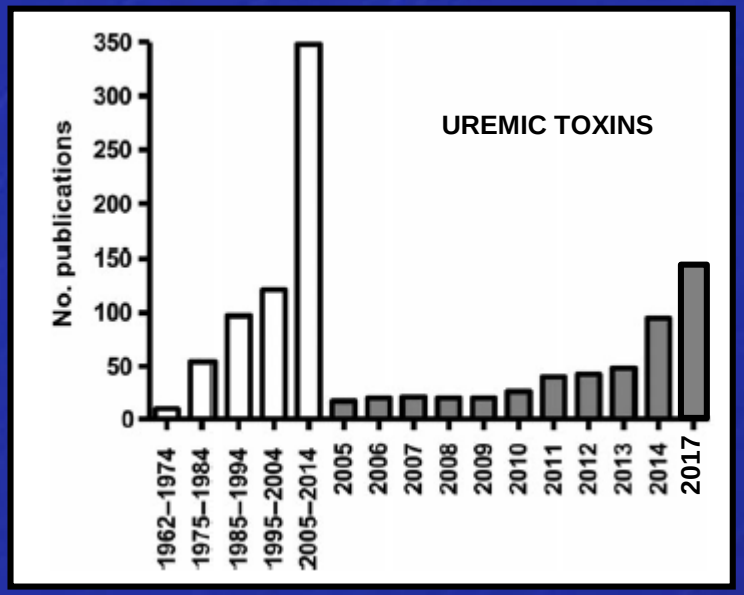
Enter: UREMIC TOXIN

Relative frequency of the use of UREMIC TOXINS



Google Books Ngram Viewer

Enter: UREMIC TOXIN



Kidney Int. 2003;63:1934-1943
Clin Kidney J. 2015;8:353-362
Lancet 2014;383:1831-1843

FREE

Solute	C_N
1-methyladenosine *μg/L*	17.1 ± 5.1/10
1-methylguanosine *μg/L*	13.7 ± 16.9/10
1-methylinosine *μg/L*	13.5 ± 3.9/10
ADMA *mg/L*	0.2 ± 0.06/6
α-keto-δ-guanidinovaleric acid *μg/L*	<30.2/66
α-*N*-acetylarginine *μg/L*	18.1 ± 24.8/16
Arab(in)itol *mg/L*	<0.6/33
Argininic acid *μg/L*	<77.0/66
Benzylalcohol *mg/L*	—
β-guanidinopropionic acid *μg/L*	<3.3/24
β-lipotropin *ng/L*	<55.3/10
Creatine *mg/L*	9.7 ± 3.3/24
Creatinine *mg/L*	<12.0/23
Cytidine *μg/L*	<468.0
Dimethylglycine *μg/L*	<381.1/33
Erythritol *mg/L*	<0.7/33
γ-guanidinobutyric acid *μg/L*	<3.6/24
Guanidine *μg/L*	<11.8/16
Guanidinoacetic acid *μg/L*	222.3 ± 79.6/24
Guanidonosuccinic acid *mg/L*	0.03 ± 0.01/16
Hypoxanthine *mg/L*	1.5 ± 0.5/145
Malondialdehyde *μg/L*	257.7 ± 81.7/30
Mannitol *mg/L*	<1.3/33
Methylguanidine *μg/L*	<7.3/24
Myoinositol *mg/L*	<10.0/8
N^2,N^2-dimethylguanosine *μg/L*	9.0 ± 4.7/10
N^4-acetylcytidine *μg/L*	57.0 ± 17.1/10
N^6-methyladenosine *μg/L*	18.5 ± 8.4/10
N^6-threonylcarbamoyladenosine *μg/L*	35.5 ± 27.2/10
Orotic acid *mg/L*	0.5 ± 1.4/30
Orotidine *mg/L*	1.2 ± 1.6/30
Oxalate *mg/L*	0.3 ± 0.1/8
Phenylacetylglutamine *mg/L*	<4.7
Pseudouridine *mg/L*	0.5 ± 5.8/30
SDMA *μg/L*	76.1 ± 21.0/66
Sorbitol *mg/L*	<0.4/33
Taurocyamine *μg/L*	<52.2/24
Threitol *μg/L*	<319.6/33
Thymine *mg/L*	—
Uracil *μg/L*	<224.0
Urea *g/L*	<0.4/23
Uric acid *mg/L*	<67.2
Uridine *mg/L*	1.5 ± 1.3/30
Xanthine *mg/L*	0.5 ± 1.4/180
Xanthosine *μg/L*	23.9 ± 12.8/10

Protein Bound

2-methoxyresorcinol *μg/L*
3-deoxyglucosone *mg/L*
CMPF *mg/L*
Fructoselysine *mg/L*
Glyoxal *μg/L*
Hippuric acid *mg/L*
Homocysteine *mg/L*
Hydroquinone *μg/L*
Indole-3-acetic acid *μg/L*
Indoxyl sulfate *mg/L*
Kinurenine *μg/L*
Kynurenic acid *mg/L*
Leptin *μg/L*
Melatonin *ng/L*
Methylglyoxal *μg/L*
N^{ε}-(carboxymethyl)lysine *mg/L*
p-cresol *mg/L*
Pentosidine *μg/L*
Phenol *mg/L*
P-OHhippuric axid *mg/L*
Putrescine *μg/L*
Quinolinic acid *mg/L*
Retinol-binding protein *mg/L*
Spermidine *μg/L*
Spermine *μg/L*

Middle Molecule

Adrenomedullin *ng/L*
Atrial natriuretic peptide *ng/L*
β_2-microglobulin *mg/L*
β-endorphin *ng/L*
Cholecystokinin *ng/L*
Clara cell protein (CC16) *mg/L*
Complement factor D *mg/L*
Cystatin C *mg/L*
Degranulation inhibiting protein I^c *μg/L*
Delta-sleep inducing peptide *μg/L*
Endothelin *ng/L*
Hyaluronic acid *μg/L*
Interleukin-1β *ng/L*
Interleukin-6 *ng/L*
κ-Ig light chain *mg/L*
λ-Ig light chain *mg/L*
Leptin *μg/L*
Methionine-enkephalin *ng/L*
Neuropeptide Y *ng/L*
Parathyroid hormone *μg/L*
Retinol-binding protein *mg/L*
Tumor necrosis factor-α *ng/L*

Enter: **"Uremic Toxins"**

Enter: **"Residual Syndrome"**

"Patients who would have died from uremia but survive because of dialysis suffer from a previously non-existent life-threatening disease that is labeled here for lack of a better term the 'residual syndrome"

Clin JASN 2012;
Sem Dialysis 2001; 14:246-251

Possible causes of the residual syndrome
1. Accumulation of large molecular weight solutes that are difficult to remove by dialysis
2. Accumulation of protein-bound small molecular weight solutes that are difficult to remove by dialysis
3. Accumulation of dialyzable solutes that are incompletely removed
4. Indirect phenomena such as carbamylation of proteins, tissue calcification, or a toxic effect of hormone imbalance
5. A toxic effect of the dialysis itself *

CONCERNS*

Residual Syndrome ????

Uremic Toxins ???

but ….

---

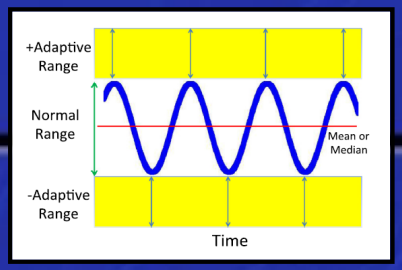
* personal

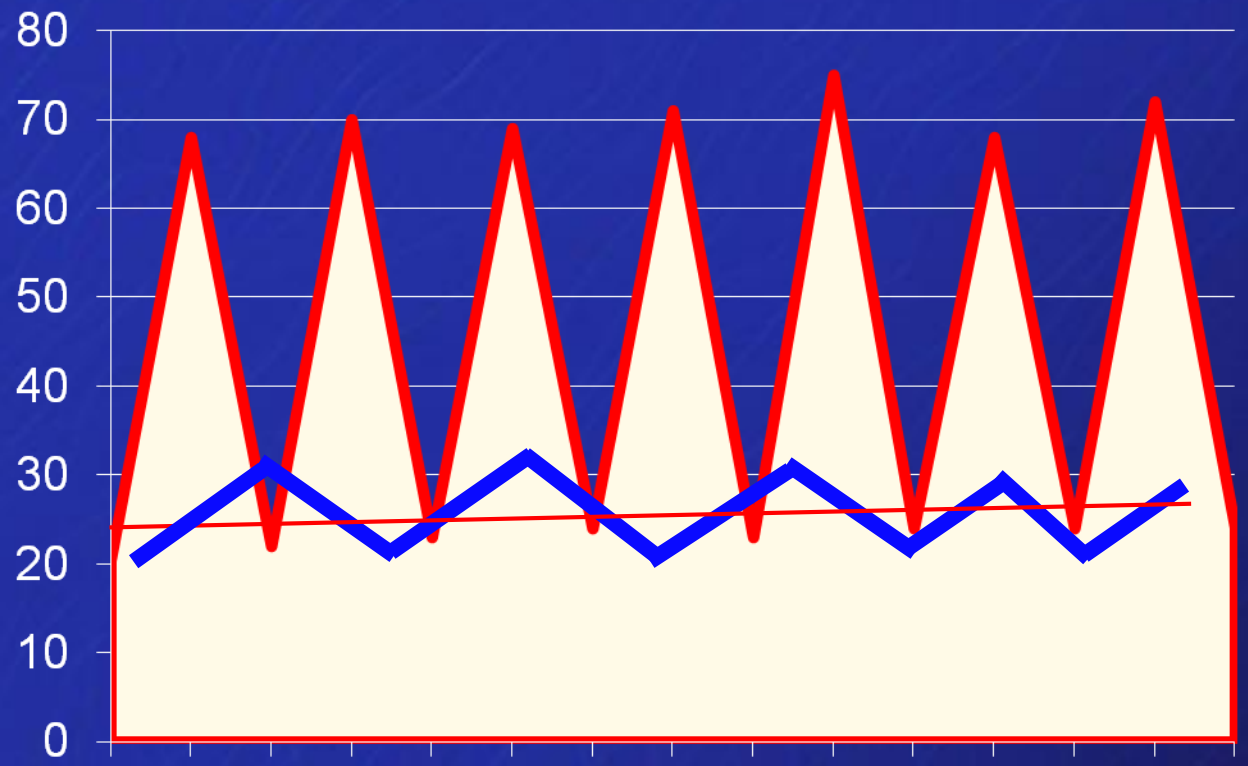
CONCERNS

1. Hemodialysis is an empiric treatment.

2. Hemodialysis is a physico-chemical process that operates in total opposition to normal physological principles.

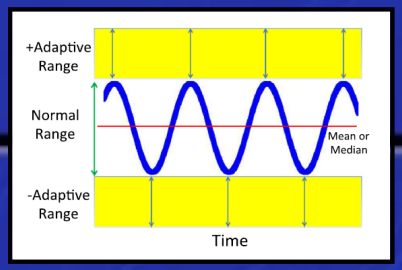
Hemodialysis

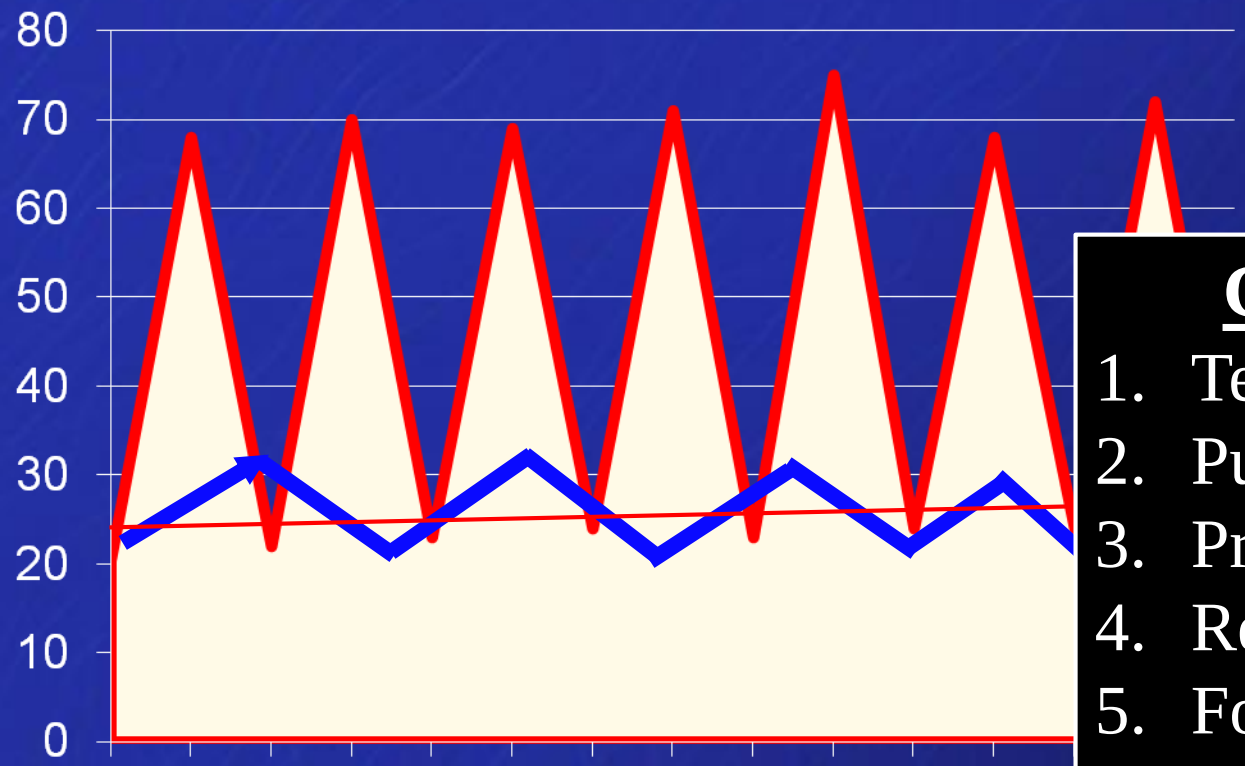




Normal
Hemodialysis

Hemodialysis





Normal
Hemodialysis

CHANGES

1. Temperature
2. Pump trauma
3. Pressure
4. Resistance
5. Foreign tubing
6. Drugs
7. Toxins

CONCERNS

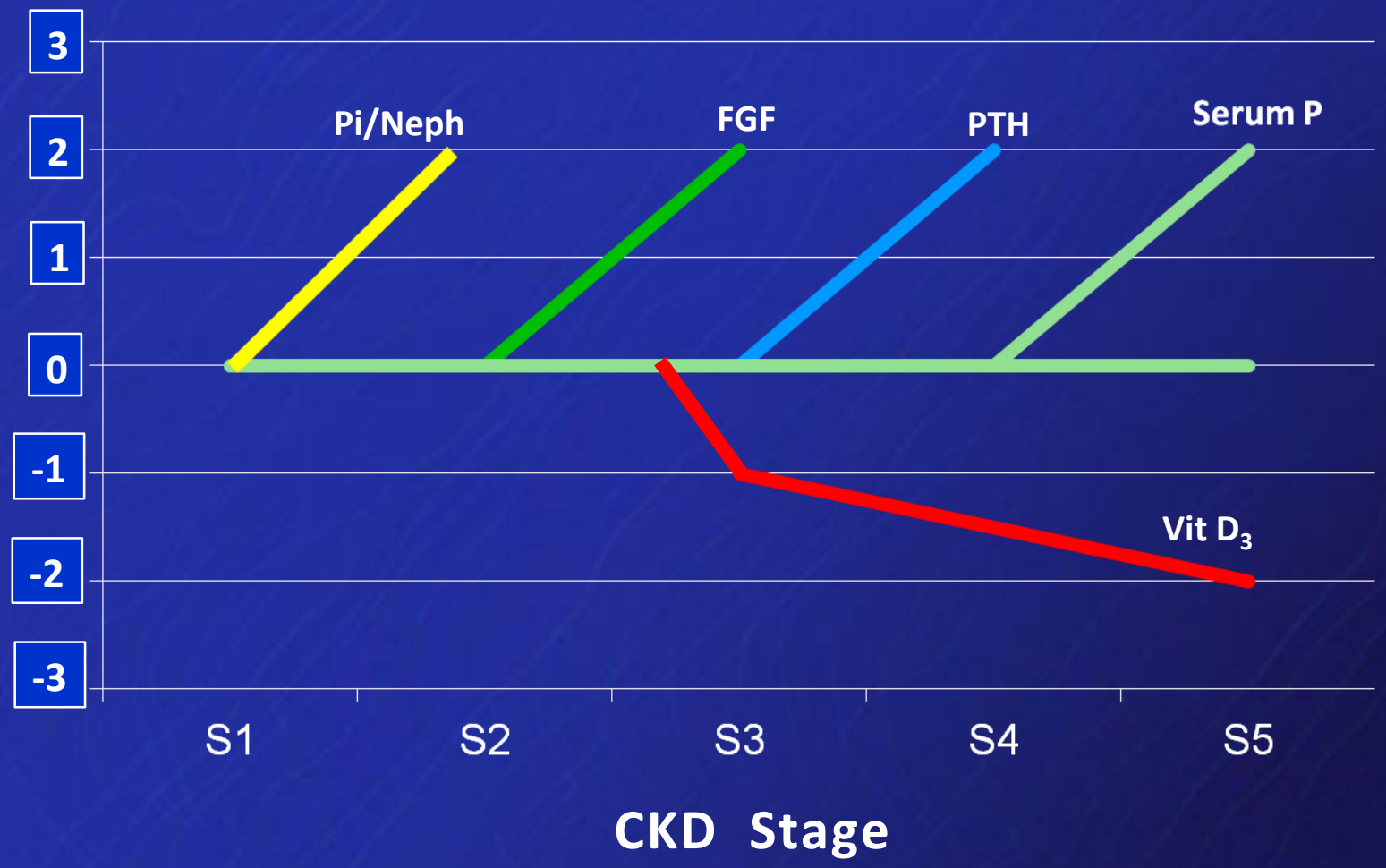
1. Hemodialysis is an empiric treatment.

2. Hemodialysis is a physico-chemical process that operates in total opposition to normal physological principles.

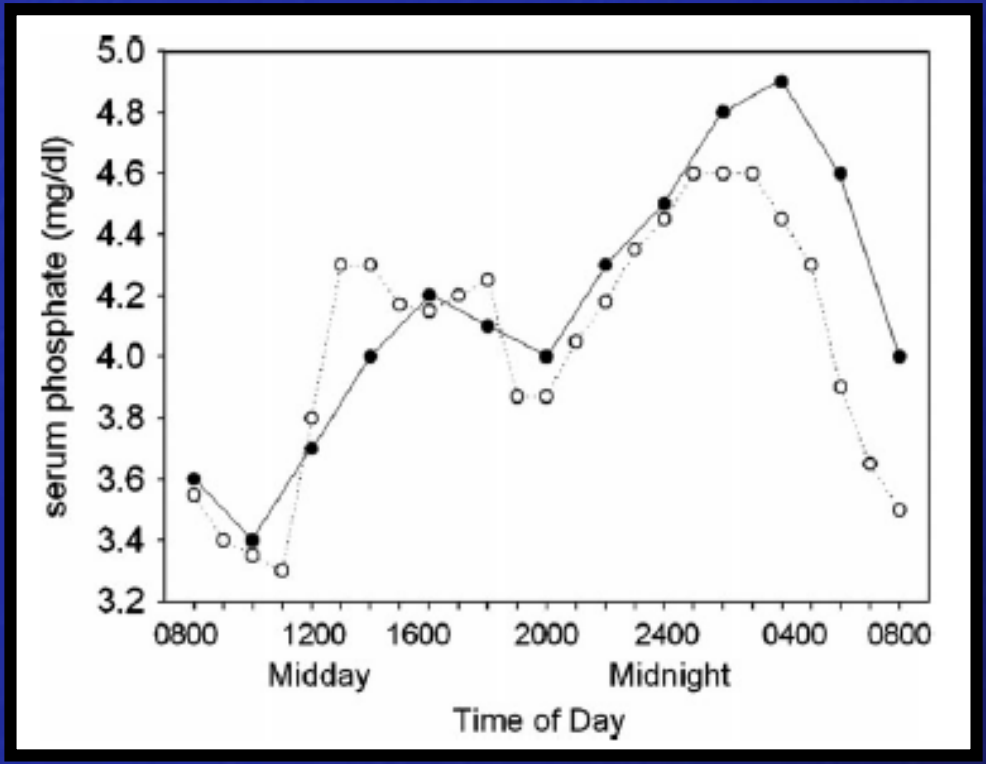
3. Hemodialysis is monitored by changes in the blood.

Hemodialysis

CKD-MBD

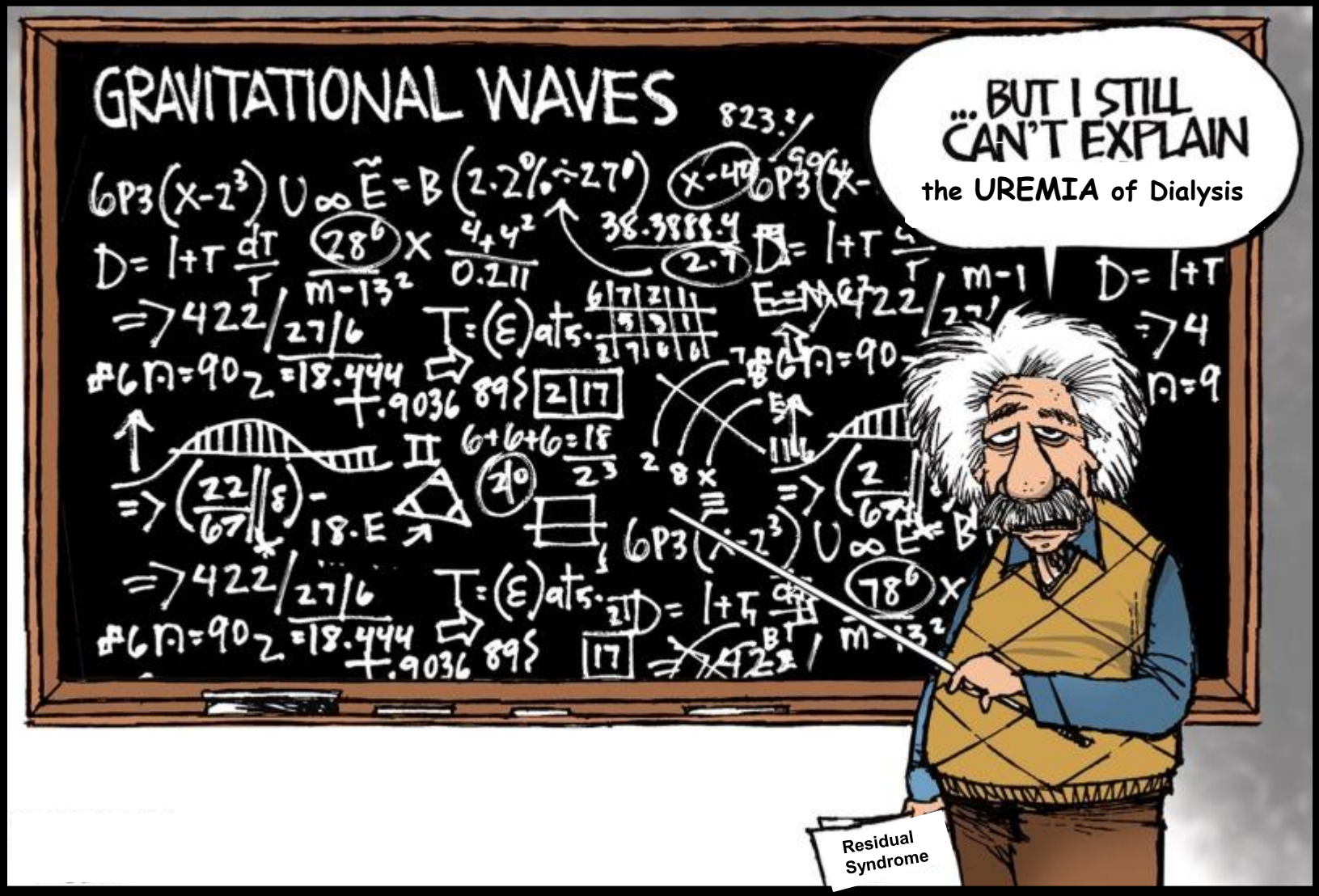


Circadian variations of serum phosphorus



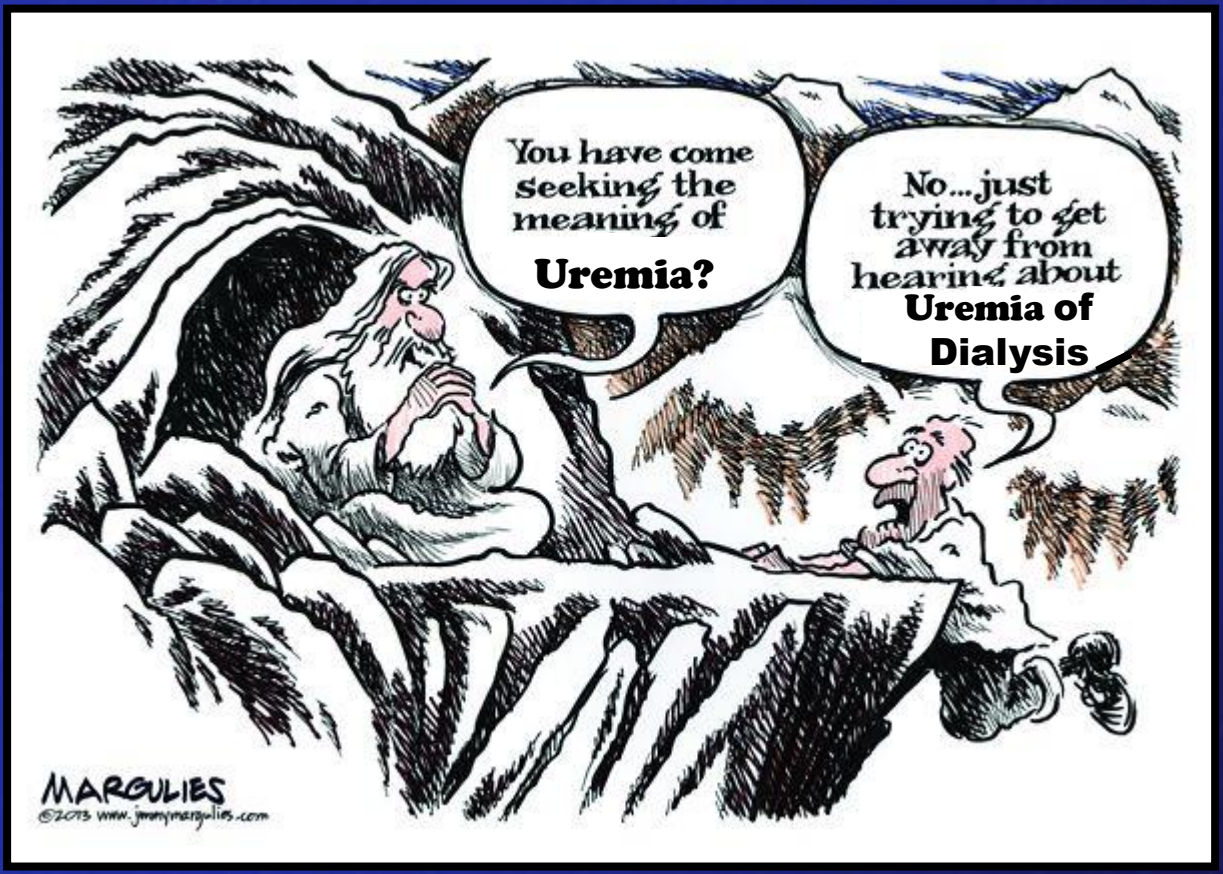
NDT 2009; 24:2321-2324

SUMMARY


GRAVITATIONAL WAVES
...BUT I STILL CAN'T EXPLAIN
the UREMIA of Dialysis
Residual Syndrome

CONCLUSION

Time to Rethink



Thank you for your attention

and the opportunity
to present at the

13th BANTAO