Anthony W Norman, PhD

Memorial lecture

presented on behalf of the Vitamin D workshop &

Roger Bouillon
MD, PhD, FRCP (London)

Clinic and Laboratory for Experimental Medicine and Endocrinology
Katholieke Universiteit Leuven
Belgium
Anthony W Norman, PhD

Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

1. *Journal of Bone and Mineral Research,*
   = American Society for Bone and Mineral Research

2. *Journal of Steroid Biochemistry and Molecular Biology*
   to be published with the Proceedings
   of the Vitamin D Workshop held in NYC May 2019
Anthony W Norman, PhD

Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Mark R Haussler, PhD
Department of Basic Medical Sciences, College of Medicine-Phoenix, The University of Arizona, Phoenix, AZ, USA

Sylvia Christakos, PhD
Departments of Microbiology, Biochemistry, and Molecular Genetics, Rutgers New Jersey Medical School, The State University of New Jersey, Newark, NJ, USA

Roger Bouillon, MD, PhD, FRCP
Laboratory of Clinical and Experimental Endocrinology, Department of Chronic Diseases, Metabolism and Ageing, KU Leuven, Leuven, Belgium
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

In memoriam AW Norman to be published in JSBMB 2020

Daniel Bikle, MD, University of California San Francisco and VA Medical Center, CA, USA

JoEllen Welsh, PhD  SUNY Distinguished Professor & Empire Innovation Professor, Environmental Health Sciences University at Albany Cancer Research Center, Rensselaer, NY 12144

Roger Bouillon, MD, PhD, FRCP
Laboratory of Clinical and Experimental Endocrinology, Department of Chronic Diseases, Metabolism and Ageing, KU Leuven, Leuven, Belgium
Anthony W Norman, PhD

Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

- Born in Ames, Iowa in 1938
- BS from Oberlin College in 1959
- MS (1961), from the University of Wisconsin, Madison
- PhD (1963) from the University of Wisconsin, Madison
  (fellow in Biochemistry & research assistant)
- Postdoctoral Fellow Dept Chemistry, UCLA 1963-64
- A member of the UCR faculty since 1963
  assistant professor and assistant biochemist ➔ professor & chairman department of biochemistry
divisional dean Biomedical sciences
emeritus professor
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

• PhD research in Madison

• Mentor: Hector F DeLuca

= Laboratory of Biochemistry of the Master of vitamin D:

~~ Tony = the “grand-student” of the famous Harry Steenbock, a pioneer in vitamin D research at Wisconsin who discovered that irradiation with ultraviolet light increased the vitamin D content of foods.
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

PhD research in Madison/Wisconsin (1961-1963)

Mentor: Hector F DeLuca

Publications:

**BIOLOGICALLY ACTIVE FORMS OF VITAMIN D3 IN KIDNEY AND INTESTINE.**

**THE SUBCELLULAR LOCATION OF H3 VITAMIN D3 IN KIDNEY AND INTESTINE.**
Norman AW, Deluca HF. Arch Biochem Biophys. 1964;107:69-77

**Vitamin D and the incorporation of [1-14C]acetate into the organic acids of bone.**

**THE PREPARATION OF H3-VITAMINS D2 AND D3--THEIR LOCALIZATION IN THE RAT.**
Early independent research in UCR (1963 onwards)

!!! Combined with postdoctoral research in the area of oxidative phosphorylation in the laboratory of Nobel Laureate Paul D Boyer at the University of LA

**Choice of research area:**

Biochemical, cellular and molecular endocrinology, and physiology of the vitamin D endocrine system

*Why his choice of vitamin D was very wise??*

➔ *End of the present lecture*
Cholecalciferol

---

7-Dehydroxycholecalciferol

++ skin (UV)

-- 7DHC-delta-7-reductase

Black box

Cures rickets

Status 1920-1930’s

Nutrition

- fish
- food + D
- milk
- meat
- others

35.0%
30.0%
15.0%
10.0%
10.0%
Dehydroxycholecalciferol

Cholecalciferol

7-Dehydroxycholecalciferol

**nutrition**

- fish
- meat
- milk
- food + D
- others

<table>
<thead>
<tr>
<th>Source</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>fish</td>
<td>35.0%</td>
</tr>
<tr>
<td>meat</td>
<td>30.0%</td>
</tr>
<tr>
<td>milk</td>
<td>15.0%</td>
</tr>
<tr>
<td>food + D</td>
<td>10.0%</td>
</tr>
<tr>
<td>others</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

**Improves intestinal calcium absorption**

**Status 1940-1960’s**

- Black box

**Cures rickets**

++ skin (UV)

-- 7DHC-delta-7-reductase
Cholecalciferol (Vitamin D3) is converted from 7-dehydroxycholecalciferol (7-DHC) in the liver through the action of 7-DHC-delta-7-reductase. This process, known as 25-hydroxylation, results in 25-hydroxycholecalciferol. This form of vitamin D then improves intestinal calcium absorption, which was a significant improvement in the 1960s. The increase in intestinal calcium absorption was further augmented by the sun's ultraviolet rays, which convert 7-DHC to vitamin D3 (cholecalciferol) in the skin.

Status in the 1960s:
- Black box: This refers to the discovery of vitamin D3's role in curing rickets, which was a significant public health achievement.
- Cures rickets: Vitamin D3 was crucial in treating rickets, a bone disease caused by vitamin D deficiency.
Hydroxycholecalciferol

Kidney (Mitoch CYP27B1)

Cholecalciferol

nutrition

++ skin (UV)

-- 7DHC-de-7-reductase

7-Dehydroxycholecalciferol

liver

(mitoch CYP27A1)
(micros CYP2D5)
(micros CYP2R1)

25- Hydroxycholecalciferol

1α,25(OH)2D●DBP

1μg

fish food + D milk meat others

35.0%
30.0%
15.0%
10.0%
10.0%
Anthony W Norman, PhD

Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

The first research advances from AW Norman’s laboratory with M Haussler as his first PhD student:

- The effect of vitamin D to stimulate intestinal calcium absorption in rachitic chickens was inhibited by actinomycin D, suggesting that unlike the water-soluble vitamins which functioned as enzyme cofactors, vitamin D action required mRNA/protein synthesis. (Science 1965)

- Dr. Norman’s group reported that after intracardiac injection of radioactively labeled vitamin D into vitamin D deficient chickens, the predominant subcellular fraction of the small intestine containing the radioactive tag was the nucleus ~ consistent with a genomic mechanism of action for vitamin D or a metabolite (Archives of Biochemistry and Biophysics, 1967)
Radioactive vitamin D (metabolite) localized exclusively to purified chromatin, further supporting a role for DNA-driven gene transcription in the molecular response to vitamin D.

The chromatin-associated, labeled sterol was extracted from intestinal chromatin and analyzed chromatographically in numerous systems, and proven to be a metabolite of vitamin D more polar than 25(OH)D and biologically active (Journal of Biological Chemistry in August 1968).
As reported in January 1969 in the Proceedings of the National Academy of Sciences of the United States of America (Proc Natl Acad Sci USA), we* discovered a “Chromosomal Receptor for a Vitamin D Metabolite.”

This DNA-binding and vitamin D metabolite–binding protein has become known as the vitamin D receptor (VDR).

* Chromosomal receptor for a vitamin D metabolite by Mark R. Haussler and Anthony W. Norman, Department of Biochemistry, University of California (Riverside)
Identification of 1,25-Dihydroxycholecalciferol, a New Kidney Hormone controlling Calcium Metabolism

D. E. M. Lawson†, D. R. Fraser†, E. Kodicek†, H. R. Morris† & Dudley H. Williams†

Dunn Nutritional Laboratory, University of Cambridge, and Medical Research Council, Milton Road, Cambridge

Identification of 1,25-Dihydroxycholecalciferol, a Form of Vitamin D₃ Metabolically Active in the Intestine

M. F. Holick, H. K. Schnoes, and H. F. DeLuca*

Department of Biochemistry, University of Wisconsin, Madison, Wis. 53706

Proc. Nat. Acad. Sci. USA
Vol. 68, No. 4, pp. 803-804, April 1971

1,25-Dihydroxycholecalciferol: Identification of the Proposed Active Form of Vitamin D₃ in the Intestine

Anthony W. Norman 1, James F. Myrtle 1, Ronald J. Miogett 1, Henry G. Nowicki 1, Vincent Williams 2, and G. Popjaš 2

1 Department of Biochemistry, University of California, Riverside 92502
2 Department of Biological Chemistry, School of Medicine, University of California, Los Angeles 90024

Science 2 July 1971: Vol. 173. no. 3991, pp. 51 - 54
Anthony W Norman, PhD

Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Chemical identification of the more polar metabolite:

1,25-dihydroxyvitamin D₃ or 1,25(OH)₂D₃

Discovery of a nuclear receptor for the active vitamin D metabolite

So by the end of 1971, 1,25(OH)₂D₃ became known as the vitamin D hormone, with the kidney as its primary endocrine gland, and active by binding and activating a nuclear receptor.
Nuclear receptor superfamily

Class II type: heterodimer
- hVDR
- mRXRα
- mRXRβ
- mRXRγ
- hRARα
- hRARβ
- hRARγ
- hTRα
- hTRβ

Class I type: homodimer
- hERα
- hERβ
- hGR
- hPR
- hAR
- hMR

AF-1 co-regulator complex
AF-2 co-regulator complex

1α,25(OH)2D3
9-cis-retinoic acid
All-trans-retinoic acid
3,3',5-triiodothyronine
Estradiol-17β
Steroid hormone (Glucocorticoid, Progesterone, Androgen, Mineralcorticoid)
Vitamin D

UV B + 7-DHC-Δ7-dehydrogenase or vitamin D

Vitamin D in muscle, fat, liver...

Vit D-25-hydroxylase (CYP2R1)

25(OH)D

DBP

25(OH)D-1α-hydroxylase

25(OH)D-24R-hydroxylase

24,25(OH)_2D
25,26(OH)_2D

25(OH)D-1α-hydroxylase

1,25(OH)_2D

Thyroid hormones

Iodide

thyreoglobulin

T₄⁻

TBG

de-iodinases
liver, muscle

rT₃

T₃

only occasional access

tissue storage in pro-precursor form

circulating precursor

biological activation or inactivation
Vitamin D

24,25(OH)₂D  1,25(OH)₂D
25,26(OH)₂D

low affinity high

Thyroid hormones

rT₃  T₃

low affinity high

nuclear receptor

RXR

(VDRE) + coactivators

TRANSACTIVATION

RXR

(TRE) + coactivators

TRANSACTIVATION

steroid receptor superfamily

heterodimerisation

similar hexanucleotide repeat but different spacer number

gene transcription
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Overview of the major contributions of Anthony W Norman (1)

- Discovery and chemical characterization of $1,25(\text{OH})_2\text{D}_3$, the vitamin D hormone

- Discovery and characterization of the vitamin D receptor (VDR)

- Description of the vitamin D-mediated intestinal calcium transport

.../...
Identification of the molecular actions of vitamin D in the intestine (1)


Identification of the molecular actions of vitamin D in the intestine (2)

Sylvia Christakos as PostDoc (1976-1980) in AW Norman’s lab:
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Christakos Silvia, postdoc at AW Norman’s lab (1976-1980)

- **Vitamin D3-induced calcium binding protein in bone tissue.**  
  Christakos S and Norman AW. Science. 1978 Oct 6;202(4363):70-1

- **Studies on the mode of action of calciferol. XIII. Development of a radioimmunoassay for vitamin D-dependent chick intestinal calcium-binding protein and tissue distribution.**  
  Christakos S, Friedlander EJ, Frandsen BR and Norman AW. Endocrinology. 1979 May;104(5):1495-503

- **Studies on the mode of action of calciferol. XVIII. Evidence for a specific high affinity binding protein for 1,25 dihydroxyvitamin D₃ (VDR) in chick kidney and pancreas.**  
  Christakos S and Norman AW. Biochem Biophys Res Commun. 1979 Jul 12;89(1):56-63

- **Radioimmunoassay for chick intestinal calcium-binding protein.**  

- **Localization of immunoreactive vitamin D-dependent calcium binding protein in chick nephron.**  
CaBP in chicks

<table>
<thead>
<tr>
<th>Group</th>
<th>Bone CaBP (ng/mg protein)</th>
<th>Duodenal CaBP (ng/mg protein)</th>
<th>Serum CaBP (ng/ml)</th>
<th>Serum Ca(^{++}) (mg/100 ml)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>-D</td>
<td>4.4 ± 1.4</td>
<td>36 ± 0.014</td>
<td>0</td>
<td>5.4 ± 0.36</td>
<td>6</td>
</tr>
<tr>
<td>+D</td>
<td>109.0 ± 22*</td>
<td>25,000 ± 4,400</td>
<td>49 ± 8†</td>
<td>8.0 ± 0.26</td>
<td>6</td>
</tr>
</tbody>
</table>

**Experiment A**

<table>
<thead>
<tr>
<th>Group</th>
<th>Bone CaBP (ng/mg protein)</th>
<th>Duodenal CaBP (ng/mg protein)</th>
<th>Serum CaBP (ng/ml)</th>
<th>Serum Ca(^{++}) (mg/100 ml)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low calcium</td>
<td>460 ± 55</td>
<td>12,000 ± 900</td>
<td>65 ± 23</td>
<td>6.6 ± 0.40</td>
<td>7</td>
</tr>
<tr>
<td>High calcium</td>
<td>101 ± 19*</td>
<td>6,400 ± 1,100</td>
<td>9.8 ± 1.8</td>
<td>9.0 ± 0.42</td>
<td>6</td>
</tr>
</tbody>
</table>

*P < .001. †This concentration of CaBP in the serum is equivalent to 1.4 ng per milligram of serum protein.

A: Fed a rachitogenic diet for 6 w +/- vitamin D
B: Fed a rachitogenic diet for 6 w and then R/ vitamin D and a low or high calcium diet

Christakos & Norman, Science 1978
VDR dependent active calcium absorption

$\text{Ca}^{2+}$

VDR

$1,25(\text{OH})_2\text{D}_3$

$\text{PMCA}_{1b}$

TRPV6 = ECaC2 = CaT1
TRPV5 = ECaC1 = CaT2

ECaC2

CaBP9K

Van Cromphaut et al., PNAS, 2001
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Overview of the major contributions of Anthony W Norman (2)

- Metabolism of vitamin D

- Chemistry of vitamin D analogs & structure function analysis
Regulation of the key enzyme, 1alpha-hydroxylase (CYP27B1)


METABOLISM OF VITAMIN D
&
Structure function analysis of vitamin D analogs

Bouillon, Okamura & Norman,
Endo Rev 1995
cited more than 1000 times up to 2019
Anthony W Norman, PhD

Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Overview of the major contributions of Anthony W Norman (3)

- Vitamin D’s action beyond the intestine:
  - endocrine pancreas
  - immune system
  - parathyroid gland
- Discovery of the biological importance of 24,25(OH)$_2$D$_3$
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Identification of action of the vitamin D endocrine system beyond the intestine

1. Endocrine pancreas
   - Vitamin D and normal insulin secretion (*Journal of Clinical Investigation*, 1981)

2. Immune system
   - Role of 1,25(OH)$_2$D$_3$ in human peripheral blood lymphocytes (*Journal of Clinical Investigation*, 1987), with Koeffler P
   - Regulation of granulocyte-macrophage colony stimulating factor (GM-CSF) by inhibition of interferon-$\gamma$ synthesis by 1,25(OH)$_2$D$_3$ (*Proc Natl Acad Sci U S A*, 1987)
   - Stimulation of 1,25(OH)$_2$D$_3$ synthesis in human bone marrow and alveolar macrophages by interferon-$\gamma$ (*Journal of Biological Chemistry*, 1987)
Clinical implications of new discoveries of the vitamin D endocrine system (4)

Showing that 1,25(OH)$_2$D$_3$ was efficacious in treating patients with renal osteodystrophy
(New England J Medicine 1972) (In collaboration with nephrologist Jack Coburn at UCLA)

Actions of 1,25(OH)$_2$D$_3$ in patients with hypophosphatemic, vitamin D resistant rickets
(New England J Medicine 1973)

Actions of 1,25(OH)$_2$D$_3$ in patients with chronic renal failure
(Ann Intern Med 1974)
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Clinical implications of new discoveries of the vitamin D endocrine system (2)

.../

2. Therapeutic effect of 1,25(OH)$_2$D$_3$ in patients with hypoparathyroidism (Lancet 1974)

Overview of the major contributions of Anthony W Norman (5)

- Paracrine system of 1,25(OH)₂D₃ local extra-renal production of 1,25(OH)₂D₃

- Structure function of vitamin D (metabolites/analogs)

- Non-genomic actions of vitamin D / 1,25(OH)₂D₃ (metabolites/analogs)

Example: lecture AW Norman in Maastricht vitamin D workshop meeting 2003
A MECHANISTIC CONUNDRUM:

HOW CAN $1\alpha,25(\text{OH})_2\text{D}_3$ MEDIATE BOTH GENOMIC RESPONSES AND RAPID RESPONSES?


Departments of Biochemistry & Chemistry
University of California
Riverside, CA
CONUNDRUM:

“A problem that is difficult to deal with.”.

Cambridge Dictionary online

“An intricate and difficult problem.”

Merriam Webster online
$1\alpha,25(\text{OH})_2\text{D}_3$ RAPID RESPONSES

- **Chondrocytes**
  - PKC activation
  - B. Boyan, Z. Schwartz

- **Myoblasts**
  - PKC activation
  - A. Russo-de Boland, R. Boland

- **Osteoblasts**
  - Intracellular Ca$^{2+}$
  - M. Lieberherr

- **Intestine**
  - Transcalcitachia
  - I. Nemere, A. Norman

- **ROS 17/2.8 cells**
  - Voltage-gated Ca$^{2+}$ channels
  - C. Farach-Carson, J. Caffrey

- **Intestine**
  - Phosphate Transport
  - C. Farach-Carson, I. Nemere

- **NB4 cells**
  - Initiation of cell differentiation
  - K. Meckling-Gill
SUMMARY

• The CMF VDR$_{Mem}$ is the classic VDR
  – Western blot analysis
  – VDR KO abrogates rapid responses
  – VDR KO greatly reduces 1$\alpha$,25(OH)$_2$D$_3$ in vitro
  – CFM VDR$_{Mem}$ has ligand specificity close to classic VDR

• Computer modeling of classic VDR-LBD suggests presence of binding mechanisms in the LBD for genomic and rapid responses
CONCLUSION

The classical VDR, or a slightly modified form of the VDR, when localized to the CMF, is responsible for many 1α,25(OH)₂D₃ non-genomic rapid responses.
ACKNOWLEDGEMENTS

UC-Riverside

- June Bishop
- Craig Bula
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- Christopher Olivera
- Matthew Mizwicki
- Bill Okamura
- Laura Zanello
- Xiaoyu Zhang

Other Institutions

- Fatima Silva (Univ. Santa Catarina, Brazil)
- Seiichi Ishizuka (Teijin-Japan)
- Roger Bouillon (KU-Leuven, Belgium)
- Hitoshi Ishida (Kyorin U., Tokyo)
- Jim Liao, (Harvard Medical School)
- Barbara Boyan (Georgia Tech/Emory)
- Zvi Schwartz (Georgia Tech/Emory)
Thank You!!
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Vitamin D science: research and publications of original data and reviews

Training of MS and PhD’s

…/…
Anthony W Norman, PhD

Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Vitamin D science: research and publications of original data and reviews

Creation of a vitamin D community

Vitamin D science policy

Role in UCR

Regulation of the key enzyme, 1α-hydroxylase (CYP27B1)


$h$-index 96 Average citations per item 43.48 Sum of Times Cited 33,390 (nearly 2 per day for 50 yrs)

Total publications in WoS: 768 (more than one per month for 50 yrs)
Anthony W Norman, PhD

Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Tony mentored 23 students who received PhD’s during his career at UCR
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

His honors include

Mead Johnson Award from the American Institute of Nutrition (1977)
MERIT award from the National Institutes of Health (1986-93)
Fellow of the American Association for the Advancement of Science (1995)
Presidential Chair in the UCR Biochemistry Department (1999-2009)
Career Award from the Vitamin D Workshop science community (2009)
1. Vitamin D science: research and publications of original data and reviews training of MS & PhD’s

2. Creation of a vitamin D community:
   - lectures on vitamin D
   - vitamin D workshops
   - vitamin D sessions at the ASBMR
   - vitamin D meeting in NIH on deltanoids and cancer 2004
   - meetings on non-genomic actions of steroid hormones

3. Vitamin D science policy

4. Role in UCR
Encyclopedia of Hormones

Editors-in-Chief
Helen L. Henry
Anthony W. Norman

Volume 1
A–F

Volume 2
G–M
Sunday  
Sep. 13, 1981

Monday  
Sep. 14, 1981

08.30 Opening remarks:  
M. VERBANCK

PLENARY SESSION I  
VITAMIN D

08.45 A.W. NORMAN  
Vitamin D metabolism

09.30 Oral presentations

11.00 Poster presentations
Cancer Chemoprevention & Cancer Treatment: Is there a role for vitamin D, 1α,25(OH)₂-vitamin D₃, or new analogs (deltanoids)?

Sponsored by The National Cancer Institute, NIH and The Vitamin D Workshop

Wednesday, November 17 – Friday, November 19, 2004
Natcher Auditorium
National Institutes of Health
Bethesda, MD

NO REGISTRATION FEE

Abstract Deadline Date: Monday, September 27, 2004

The Scientific Program includes:
30 Invited Speaker Presentations
8 Promoted Speaker Presentations (to be chosen from submitted abstracts)
4 Poster Sessions (poster board size = 4' x 6')
6 Young Investigator Travel Awards

Organizing Committee:
Anthony Norman, Riverside, CA, USA
J. Carl Barrett, National Cancer Inst., Bethesda, MD USA
Roger Bouillon, Leuven, Belgium
Michael Sporn, Hanover, NH, USA

Check the website for meeting updates including travel and housing information and all necessary forms:
http://vitamind.ucr.edu/Cancer&CancerChemo.htm

Contact Information: vitamind@ucr.edu
1. Vitamin D science: research and publications of original data and reviews training of MS & PhD’s

2. Creation of a vitamin D community:
   - lectures on vitamin D
   - **Vitamin D Workshops**
     - vitamin D sessions at the ASBMR
     - vitamin D meeting in NIH on deltanoids and cancer 2004
     - meetings on non-genomic actions of steroid hormones

3. Vitamin D science policy

4. Role in UCR
History of Vitamin D Workshop

Vitamin D Workshop = Non-profit organization established in 1974.

Dedicated to disseminating scientific research and policy on the biology and health implications of Vitamin D and Vitamin D deficiency.
ARTICLES OF INCORPORATION
OF
VITAMIN D WORKSHOP

Article I

The name of this corporation is Vitamin D Workshop.

Article II

This is a nonprofit corporation organized solely for scientific and educational purposes pursuant to the General Nonprofit Corporation Law of the State of California, specifically, Part I of Division 2 of Title 1 of the Corporations Code.

Name        Residence
Anthony W. Norman, Ph.D.  2009 Elsinore Road
                            Riverside, California
Jack W. Coburn, M.D.     657 Lochman Lane
                            Pacific Palisades, California 90272
Helen L. Henry, Ph.D.     2099 Elsinore Road
                            Riverside, California

IN WITNESS WHEREOF, we, the undersigned, being the persons named above as first trustees, have executed these Articles this day of April, 1977.

Anthony W. Norman, Ph.D.
Jack W. Coburn, M.D.
Helen L. Henry, Ph.D.

STATE OF CALIFORNIA
COUNTY OF LOS ANGELES
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

The Vitamin D workshop mission

“Facilitate communication between chemists, biologists, biochemists, nutritionists, veterinary experts and physicians from all medical disciplines, including not only those treating bone and mineral diseases, but virtually all subspecialists from dermatologists to epidemiologists, and from pediatricians to geriatricians.

To bring together these groups of people with different “languages - literally and figuratively” and make them understand the message of togetherness rather than division is a mission that Tony again and again fulfilled with compassion and brilliance*.”

* JBMR in memoriam 2019
History of vitamin D workshops

• 1st - Frankfurt, West Germany (1973)
• 2nd - Wiesbaden, West Germany (1974)
• 3rd - Asilomar, CA, USA (1977)
ABSTRACTS

ORGANIZING COMMITTEE

A. W. Norman, Ph.D., Chairman
Department of Biochemistry
University of California
Riverside, CA 92502

J. W. Coburn, M.D., Secretary
Veterans Administration
VA Hospital, Wadsworth
Wilshire and Sauntere Blvds.
Los Angeles, CA 90073

H. F. DeLuca, Ph.D.
Department of Biochemistry
University of Wisconsin-Madison
College of Agricultural and Life Sciences
Madison, WI 53706

D. Fraser, M.D.
The Hospital for Sick Children
555 University Avenue
Toronto, 2, Canada

H. G. Grigoleit, M.D.
Medizinische Abteilung
Hoechst AG Werk Albert
Postfach 12 9101
D - 62 Wiesbaden 12 West Germany

K. Schaefer, M.D.
St. Joseph-Krankenhaus 1
Medizinische Abteilung II mit
Nephrologie und Dialyse
1 Berlin 42 (Tempelhof)
Baumerplan 24, West Germany
History of vitamin D workshops

• 1st - Frankfurt, West Germany (1973)
• 2nd - Wiesbaden, West Germany (1974)
• 3rd - Asilomar, CA, USA (1977)
• 4th - Berlin, West Germany (1979)
• 5th - Williamsburg, VA, USA (1982)
• 6th - Merano, Italy (1985)
• 7th - Rancho Mirage, CA, USA (1988)

1-7th: co-organizors include: AW Norman, HF DeLuca, J Coburn, D Fraser, HG Grigoleit, D v Herrath, T Suda
History of Vitamin D Workshops (2)

8th - Paris, France (1991)

Last minute rescheduled from February to July 1991 because of Gulf War
History of Vitamin D Workshops (3)

8th - Paris, France (1991)
9th - Orlando, FL, USA (1994)
Leuven lab dinner during the Nashville meeting
History of vitamin D workshops

• 8th - Paris, France (1991)
• 9th - Orlando, FL, USA (1994)
• 10th - Strasbourg, France (1997)
• 11th - Nashville, TN, USA (2000)
• 12th - Maastricht, Netherlands (2003)
• 13th - Victoria, BC, Canada (2006)
• 14th - Brugge, Belgium (2009)

• 8th-15th: co-organizers include: AW Norman, M Thomasset and R Bouillon
<table>
<thead>
<tr>
<th>Workshop number</th>
<th>Date</th>
<th>Number of delegates</th>
<th>Number of countries</th>
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<td>I</td>
<td>October 1973</td>
<td>56</td>
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<tr>
<td></td>
<td>Frankfurt, West Germany</td>
<td></td>
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<td>II</td>
<td>October 1974</td>
<td>221</td>
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<td></td>
<td>Wiesbaden, West Germany</td>
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<td>III</td>
<td>January 1977</td>
<td>332</td>
<td>20</td>
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<td></td>
<td>Asilomar, California, USA</td>
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<td>IV</td>
<td>February 1979</td>
<td>402</td>
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<td></td>
<td>Berlin, West Germany</td>
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<td>V</td>
<td>February 1982</td>
<td>455</td>
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<td>Williamsburg, Virginia, USA</td>
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<td>VI</td>
<td>March 1985</td>
<td>474</td>
<td>27</td>
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<td></td>
<td>Merano, Italy</td>
<td></td>
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<tr>
<td>VII</td>
<td>April 1988</td>
<td>381</td>
<td>24</td>
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<td></td>
<td>Rancho Mirage, California, USA</td>
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<tr>
<td>VIII</td>
<td>July 1991</td>
<td>595</td>
<td>32</td>
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<tr>
<td></td>
<td>Paris, France</td>
<td></td>
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<tr>
<td>IX</td>
<td>May 1994</td>
<td>502</td>
<td>31</td>
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<td></td>
<td>Orlando, Florida, USA</td>
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<td>X</td>
<td>May 1997</td>
<td>571</td>
<td>37</td>
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<tr>
<td></td>
<td>Strasbourg, France</td>
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<td>XI</td>
<td>May 2000</td>
<td>376</td>
<td>30</td>
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<td>Nashville, Tennessee, USA</td>
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<td>XII</td>
<td>July 2003</td>
<td>323</td>
<td>30</td>
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<td>Maastricht, The Netherlands</td>
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<td>XIII</td>
<td>April 2006</td>
<td>332</td>
<td>24</td>
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<td>Victoria, BC, Canada</td>
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<td>XIV</td>
<td>October 2009</td>
<td>420</td>
<td>35</td>
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<td></td>
<td>Brugge, Belgium</td>
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</table>
Renewed leadership of the Vitamin D Workshop

Planning phase: Description of the Composition and Operation of the Vitamin D Workshop

Workshop Executive Committee (WEC)

By Tony Norman, Helen Henry & Roger Bouillon
Final Version June 7, 2012

“We propose creation of a Vitamin D Workshop Executive Committee (WEC) and a Vitamin D Workshop Program Advisory Committee (PAC) that will collectively have responsibility for planning and presenting an annual 2 - 3 day Vitamin D Workshop in the days immediately preceding the US Endocrine Society meeting (at present in the month of June). We keep the option open to organize from time to time a similar type meeting in Europe instead of in North America.”
The remaining funds were transferred to the new organization.

This was emotionally not an easy decision for Tony, because the workshop was his intellectual “baby.”

However, this magnanimous decision perfectly reflects Tony’s attitude and lifestyle: science and scientific transparency and integrity come well before personal “ego” or status.

* cited from JBMR 2019 “in memoriam”
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

History of Vitamin D Workshops (5)

15th - Houston, TX, USA (2012)
16th - San Francisco, CA, USA (2013)
17th - Chicago, IL, USA (2014)
18th - Delft, Netherlands (2015)
19th - Boston, MA, USA (2016)
20th - Orlando, FL, USA (2017)
21st - Barcelona, Spain (2018)
22nd - New York City, NY (2019)

After 15th meeting: creation of a vitamin D Workshop Executive Committee of about 8 rotating members with AWNorman and R Bouillon as ex-officio non-voting members
History of Vitamin D Workshops (6)

The WEC is planning the next Vitamin D Workshop which will be held on the Gold Coast of Australia in August 2020.

The 2020 meeting will be chaired by Dr. Peter Ebeling of Monash University, Melbourne, Australia
VITAMIN D WORKSHOP

2014 17th Workshop
June 17th-20th
(EMDO 2014, June 17th-20th)
Chicago, IL

2015 18th Workshop
April 21st-24th
Delft, The Netherlands

2016 19th Workshop
March 28th-31st
(EMDO 2016, April 1st-4th)
Boston, MA
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

1. Vitamin D science: research and publications of original data and reviews

2. Creation of a vitamin D community:

3. Vitamin D science policy

4. Role in UCR
Editorial

14th Vitamin D Workshop consensus on vitamin D nutritional guidelines☆

Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

VDW & WHO involvement to eradicate rickets

**Joint WHO – VDW symposium in Delft 2015**

Review Prevention and consequences of vitamin D deficiency in pregnant and lactating women and children:

A symposium to prioritise vitamin D on the global agenda

Inez Schoenmakers,*, John M. Pettifor, Juan-Pablo Peña-Rosas, Christel Lamberg-Allardt, Nick Shaw, Kerry S. Jones, Paul Lips, Francis H. Glorieux, Roger Bouillon

Early independent research in UCR (1963 onwards)

!!! Combined with postdoctoral research in the area of oxidative phosphorylation in the laboratory of Nobel Laureate Paul D Boyer at the University of LA

Choice of research area:

Biochemical, cellular and molecular endocrinology, and physiology of the vitamin D endocrine system

Why his choice of vitamin D was very wise???

→ End of the present lecture
Francisci Glissonii
Med. Dobl. & Tertill. in Acad. &
Collegii Medici in Lond. Soci.
TRACTATUS
DE
RACHITIDE
Sive
MORBO PUEBRI,
Subiecta itinere Observationem
GEORGII BATE
&
AHASUERI REGEMORTERI.
Medicinae Doctorum, eademque Collegii
Londinii in Societatem,
Edita Postremo.

HAG. COMITIS,
Apud ARNOLDUM LEERS,
M. DC. LXXXII.

DISPUTATIO MEDICA
INAUGURALIS,
De E
Morbo puerili Anglorum,
quem patrio idioma indigenae
vocant
The Rickets,
L. V. A.M
Deo Suppetias ferente,
Ex authentica Nobleissimi Rerum Negotii Magnifici,
D. JOHANNIS POLYANDRI KERCHOVEN
SS. Theologiae Doctoris, eademque Facultatis in Mis-
Brittania Acad. Legis Loci Pedenione primari,
Deo Regia Filiatione Medicae, & Anglicani Secretis
Academiae confessa.
Pro Grafo Doctoris, familiisque in Medicinae Privilegiis
consecratis,
Disertationem proponit
DANIEL WHISTLER, Anglor.
Saxonicus - Oxoniensis,

LUODVNI BATAFORUM. 
Ex Offini
WILHEMI CHRISTIANI BXXII. 1641.
Rickets

Skeletons affected by rickets, 1749.

Credits Wellcome Library, London.

Rickets is a deficiency disease caused by a lack of minerals in the bones. In the 1800s the disease was widespread in the poor districts of industrial cities in Great Britain and the United States.
Prevalence of rickets in early 20th century

Hess 1917: all “negro” children living in New York have some degree of rickets

Schmorl 1909: mild and severe rickets at autopsy (1901-1908) of young children: 94% and 45%, respectively, in Dresden (Germany)

Follis et al, 1952: based on autopsy data of children, respectively, aged 0-2 years (Baltimore area 1926-42)
56% and 72% of all white or “negro” children have some form of rickets,
8% and 33% had severe rickets
Rickets in early 20th century (1)
Cod liver oil and cure of rickets

- Hess (US) – JAMA 1917;69:1583
  Clinical non randomized trial of AfroAmerican children in NY proved efficacy of cod liver oil to prevent/cure rickets

Confirmed by:

- Mellanby family (UK) – Lancet 1919
Huldschinsky, 1919 : Rickets in children can be cured by artificial UV light (mercury vapor lamp)

&

Hess, 1921 JAMA, 77:39 : Infantile rickets cured by artificial light and sunlight

Harry Steenbock (US) 1924 : UV-irradiated vegetable oil can cure rickets (patent Wisconsin University)
“within the next decade* or even sooner, it [rickets] will be almost completely eradicated, so that it will become as rare as infantile scurvy since the wide-spread use of orange juice”

* [text written in 1929]
### Examples of reported prevalence of rickets in Africa, Middle East and Asia*

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Rate%</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mongolia</td>
<td>1998</td>
<td>70</td>
<td>Rickets signs</td>
</tr>
<tr>
<td>Tibet</td>
<td>1994</td>
<td>66</td>
<td>Rickets signs</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>1997</td>
<td>42</td>
<td>X-rays</td>
</tr>
<tr>
<td>Yemen</td>
<td>1987</td>
<td>27</td>
<td>–</td>
</tr>
<tr>
<td>Turkey</td>
<td>1994</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1998</td>
<td>9</td>
<td>Rickets signs</td>
</tr>
<tr>
<td>Iran</td>
<td>1975</td>
<td>15</td>
<td>X-rays</td>
</tr>
<tr>
<td>China</td>
<td>1977–83</td>
<td>47</td>
<td>Rickets signs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.7</td>
<td>X-rays/biochem</td>
</tr>
<tr>
<td>The Gambia (West Kiang)</td>
<td>2007</td>
<td>3.3</td>
<td>Rickets signs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>Physician exam</td>
</tr>
<tr>
<td>Bangladesh (Chittagong)</td>
<td>2008</td>
<td>2.2</td>
<td>Rickets signs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0</td>
<td>X-rays</td>
</tr>
</tbody>
</table>

*Prentice

P: population sample,
H: hospital-based sample,
H*: children admitted to hospital with pneumonia,
V: children attending for vaccination.

* Prentice
Memorandum for WHO to ERADICATE nutritional RICKETS BEFORE 2030

1st step: appoint a task force on behalf of ISE, IFMRS, US and EU Pediatric Endo Societies and vitamin D workshop to prepare a motivated memorandum for WHO

2nd step: convince leadership of WHO in Geneva

3rd step: as many as possible countries, member of WHO, ask WHO to implement plan to eradicate nutritional rickets in the word before 2030

4th step: approval of implementation plan by General Assembly of WHO

5th step: support by other agencies and foundations such as UNICEF, Bill & Melinda Gates and Thrasher foundations to support the implementation of this plan

6th step: monitoring implementation plan and progress

*** ~ project in line with the WHO and its member states project to eradicate iodine deficiency disorders
Vitamin D Bouillon, NatRevEndo 2017

*----------------------------------------→ e.g. Chapuy et al

*----------------------------------------→ ViDA - VITAL
<table>
<thead>
<tr>
<th>Serum 25OHD nmol/L</th>
<th>&lt; 25/30 (%)</th>
<th>&lt; 50 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>World overview 1</td>
<td>6.7 %</td>
<td>37 %</td>
</tr>
<tr>
<td>US: NHANES 2010 data 2 (&gt; 12 yrs)</td>
<td>6.7 %</td>
<td>26 %</td>
</tr>
<tr>
<td>EU countries (adults) 3</td>
<td>13 %</td>
<td>40 %</td>
</tr>
<tr>
<td>Middle East/N Africa 4</td>
<td>~ 50 %</td>
<td>90 %</td>
</tr>
<tr>
<td>Iran &amp; Jordan</td>
<td>~ 50 %</td>
<td>90 %</td>
</tr>
<tr>
<td>African countries 5</td>
<td>&lt; 0.1%</td>
<td>7 %</td>
</tr>
<tr>
<td>China 6</td>
<td>~ 37 %</td>
<td>~ 72 %</td>
</tr>
<tr>
<td>Mongolia 4</td>
<td>~ 50 %</td>
<td></td>
</tr>
</tbody>
</table>

1 Hilger 2014 168,000 subjects from 44 countries
2 Schleicher et al AJCN 2016 (adjusted 25OHD method)
3 Cashman et al EJCN (adjusted 25OHD method)
4 Arabi et al NatRevEndo 2014
5 Durazo-Arvisu et al AJCN 2014 (Ghana, Seychelles)
6 Zhang et al Nutr 2013 (estimated from meta analysis in adults)
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

1. Vitamin D science: research and publications of original data and reviews
2. Creation of a vitamin D community:
3. Vitamin D science policy
4. Role in UCR & other science organizations
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019): Summary

1. Biochemist and Scientist
2. Mentor and distinguished professor
3. Principal Steward of the vitamin D science
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019): Summary

1. Biochemist and Scientist

- major contributions in clarifying the black box of how vitamin D works to cure rickets:
  - from a black box in 1920 to a complex endocrine system in 2020
- Crucial contributions in understanding of genomic and non-genomic actions of vitamin D
- author of > 700 pubmed publications with > 30,000 citations and a H index of nearly 100

2. .../...
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019): Summary

2. Mentor and distinguished professor

- mentor of a very large number of PhD students
- author of several handbooks and book chapters
- major role in UCR and science organisations/journals

.../...
3. Principal Steward of the vitamin D science

- created a real vitamin D community by

  Vitamin D Workshop from 1973 – today and prospering – THE leading science meeting on this nutrient and hormone

  organiser of other vitamin D related meetings (NIH – ASBMR meetings – non-genomic meetings

- Defining and supporting science policies for optimal use of vitamin D
  - general public
  - specific focus on project on eradication of rickets
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Message from the Vitamin D Workshop

&

Dan Bikle
Memories of Tony Norman
By Daniel Bikle

• I was a medical student in the 60’s working in the Rasmussen lab when I became interested in vitamin D.

• Tony had recently started his lab in Riverside having moved from Madison in 1963.

• In those days the vitamin D community was pretty small and dominated by Tony and Hector DeLuca.

• But exciting developments were emerging as vitamin D metabolism to its active metabolites, most especially 1,25(OH)₂D, and discovery of its genomic actions such as the induction of calbindin and cloning and sequencing of the vitamin D receptor started to galvanize the field.

• Thus by the early 70’s Tony realized the time had come to bring the now blossoming vitamin D community together.
Memories of Tony Norman
By Daniel Bikle

• After two workshops in Europe, the Vitamin D workshop came to the States, in particular to Asilomar in 1977.

• What a lovely setting. I was now in San Francisco having completed my medical and graduate school training but still pursuing my interests in vitamin D.

• Tony and Helen had recently given birth to Derek, and my wife and I to our first child. So some bonding of proud parents contributed to the atmosphere.

• The workshops starting with Asilomar were every 3 years and always in great locations. I did not miss a one. They really forged the international vitamin D community.
Memories of Tony Norman  
By Daniel Bikle

- With the discovery of the vitamin D receptor in most tissues and recognition that vitamin D affected many physiologic processes with potentially wide clinical application, this community had grown considerably and with great diversity.

- Tony, recognizing this growth and diversity while also wanting to expand the leadership, decided to reorganize the VDW by creating the Workshop Executive Committee with members serving terms of 3 years, to help organize the workshops.
Memories of Tony Norman
By Daniel Bikle

• Tony, recognizing the growth and diversity of the vitamin D field while also wanting to expand the leadership, decided to create a Workshop Executive Committee with members serving terms of 3 years, to help organize the workshops.
1. Summary

2. Personal notes from Roger Bouillon

From 1974 – 1981 to 2019
December 7, 1981

Dr. Roger Bouillon
Katholieke Universiteit te Leuven
Rega-Instituut
Minderbroedersstraat 10
Leuven, BELGIUM 3000

Dear Dr. Bouillon:

This is written on behalf of the faculty of the Department of Biochemistry at the University of California, Riverside to request your assistance in evaluating the scientific record and status of one of our faculty members, Anthony W. Norman. Dr. Norman is being considered for advancement and outside opinions from outstanding individuals with knowledge of the candidate's research are an important consideration in our deliberations. Enclosed is a copy of Dr. Norman's current bibliography. We would appreciate comments based on his published record and on personal contact.

The information you submit will be maintained in confidence pursuant to University policy. Although on rare occasions, disclosure of confidential personnel records may be required by law, the University will attempt to maintain confidentiality to the fullest extent possible. I would appreciate receiving your letter by the end of the year.

Thank you for help in this matter.

Sincerely,

Jolinda A. Traugh, Chair
Department of Biochemistry

JAT:mv
Enclosure
Vitamin D and bone health

Conclusions (1)

- Osteoporotic fractures can be reduced by about 20% by calcium
  +800 IU vitamin D

Vitamin D 800 IU will increase serum 25(OH)D 20 ng/mL.

25(OH)D 20 ng/mL = 50 nmol/L in >99% of the population.
pictures taken after the Vitamin D workshop Strasbourg 1997
Anthony W Norman, PhD
Biochemist, Mentor, Distinguished Professor and Principal Steward of Vitamin D Science (1938–2019)

Message from the VDW
The Vitamin D Workshop and the vitamin D community commemorate

Anthony W Norman, PhD, (1938-2019)

Biochemist, Mentor, Distinguished Professor

for his major contributions in vitamin D research and for organizing the premier scientific meeting in the discipline of vitamin D

(co) Chairpersons of Houston to Gold coast VDWs 2012-2020
Bright sunny future for vitamin D

Thank you Tony for making this possible!!!