

Karl Paul Link: emeritus professor of biochemistry. 1946/1999

[Madison, Wisconsin]: UW Communications, 1946/1999

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150 YEARS

UNIVERSITY OF WISCONSIN • SINCE 1848



Throughout the university's history, students have engaged in a wide variety of extracurricular activities that enhance the academic experience. Water skiing on chairs never really caught on, but the Memorial Union started the Hoofers Club in 1931 to create an outlet for campus recreation buffs. Starting with skiing, the club soon expanded into a smorgasbord of seven outdoor sports groups, offering stress-burning experiences from rock climbing to horseback riding. Today, its sailing club is the third-largest university sailing club in the nation, filling Lake Mendota with a gorgeous tapestry of sails each summer — not bad for a landlocked cow college.

A global reunion

Alumni convocation planned in May seeks participants from all schools, colleges

Jeff Iseminger

nternational alumni of UW-Madison representing virtually all of the university's schools and colleges will return to Madison May 3-7 for a public convocation.

The International Alumni Convocation, titled "A Global Perspective for the 21st Century," will be held on campus and at the Monona Terrace Convention Center. Drawing leaders in education, business and government from 30 countries, it is one of the events celebrating the 150th anniversary of UW-Madison's founding.

Keynoters and panels will address these topics during the week's morning sessions at Monona Terrace:

- Monday, May 3
- Science and technology transfer
- Tuesday, May 4
 Growth and the environment
- Wednesday, May 5
 Managing the global economy

- Thursday, May 6
- Local culture, politics and globalization
- Friday, May 7
- The global university

Speakers will include Yoshiyuki Kasai, president of the Central Japan Railway and manager of the famous Bullet Train; H. Steve Hsieh, vice chairman of the National Science Council of Taiwan; and Chai-Anan Samudavanija, judge of Constitutional Court and headmaster of Vajiravudh College in Thailand.

Faculty and staff may attend the morning sessions for \$25 a day, which includes lunch. Students may attend morning sessions free of charge (lunch available for \$15) if they register on a space-available basis.

For program and registration details, call 262-3152, or e-mail: interalumcon@fac-staff.wisc.edu. Visit the convocation Web site at: www.wisc.edu/intl-conv/.

RESOURCES

Check out the campus Sesquicentennial Calendar, listing institutional, school, college, departmental and area activities that will occur during our celebration. Look for the latest updates and other information at: www.uw150.wisc.edu.

FOR MORE INFORMATION

If you have any questions regarding sesquicentennial planning, you may direct them to a member of the sesquicentennial staff: Peyton Smith, sesquicentennial coordinator, 265-3044, or Cathy Davis Gray. 262-4315. Both are in 96 Bascom Hall.

Sesquicentennial Events

Public events and exhibits

April

6 Tuesday

LANDSCAPE FOR LEARNING

"Campus Management and the Environment." David Drummond, Safety Department, and Daniel Einstein, Environmental Management Program. Union South (TITU), noon.

7 Wednesday

NATIONAL SERVICE LEARNING CONFERENCE

CONFERENCE
"Envisioning Public Service in the 21st Century." A conference to examine the original public service mission of land-grant institutions and to redefine that mission for the next century. Memorial Union, Through April 9. For more information: visit http://wiscinfo.doit.wisc.edu/calsoutreach/morgridge or call 265-2407.

10 Saturday

FRENCH AND ITALIAN PRESENCE IN WISCONSIN

A conference focusing on French and Italian culture in the history of Wisconsin and the University of Wisconsin. State Historical Society, Information: 262-3941.

13 Tuesday

LANDSCAPE FOR LEARNING

"Visions of the Built Campus." Bruce Braun, Facilities Planning and Management; John Harrod, Physical Plant; and Lori Kay, Transportation Services. Union South (TTTU), noon.

20 Tuesday

LANDSCAPE FOR LEARNING

"Visions of the Natural Campus." Greg Armstrong, Arboretum; Cathie Bruner, Campus Natural Areas; Robert Hendricks, Campus Planning; and Robert Ray, Campus Natural Areas Subcommittee. Union South (TITU), noon.

23 Friday

11TH ANNUAL INSTITUTE ON AGING COLLOQUIUM

Sessions presented by UW-Madison faculty and researchers on a wide variety of recent aging studies. The Pyle Center, Information: 262-1818.

DIVERSITY IN TEACHING LAW

A symposium celebrating the 25th anniversary of the William H. Hastic Program, which provides fellowships and academic support to talented minority lawyers planning to teach law. April 23-24. Information: 265-2804, or e-mail: pshollen@facstaff. wisc.edu.

27 Tuesday

LANDSCAPE FOR LEARNING

"The Campus as a Learning Environment." Daniel Einstein, Environmental Management Program; Evelyn Howell, Department of Landscape Architecture; and Thomas Yuill, Institute for Environmental Studies. Union South (TITU), noon.

30 Friday

SESQUICENTENNIAL LECTURE

"Trends in Imaging for the 21st Century." Elizabeth V. Patton, Kodak. Sponsored by Chemistry, Chemical Engineering, and Materials Science. 1361 Chemistry Bldg., 3:30 p.m.

Exhibits

ENGINEERING PHOTO EXHIBIT

"Engineering Time." Scenes from the college's rich history; 23 images span 1881-1998. East wall, 1610 Engineering Hall. Exhibit runs through the year.

SCHOOL OF HUMAN ECOLOGY STUDENT EXHIBITION

Exhibits from landscape architecture, interior design, and textile and apparel design. Through May 13.

WISCONSIN UNION GALLERIES

"Student Purchase Award Retrospective," Highlights from more than 70 years of collecting work from the Annual Student Art Show. This exhibition is curated by the Wisconsin Union Directorate Art Committee. Theater Gallery. April 1-May 2.

FLASHBACK

HISTORICAL HIGHLIGHTS

At the beginning of the Depression, UW law students began providing legal services to indigent people, establishing a tradition of public-interest law that other schools would seize in the 1960s. By 1974, the law school made public work a formal part of its instruction, creating the Center for Public Representation, which provides free legal assistance to health-care consumers and elderly, disabled and low-income people. ... Sweet corn crops quintupled from 1930 to 1950 in Wisconsin, thanks to UW hybrids that adapted well to low temperatures and short growing seasons. And as they have with corn, UW researchers have managed to put on firm ground other crops once ravaged by disease or limited by climate. In fact, almost everything in a Wisconsin picnic has some UW history to tell. UW-inspired cranberries yield an early harvest and a deep-red color; its beans and peas are resistant to three major diseases; and its carrots have a genetic boost of beta carotene. UW research has even helped Wisconsin farmers grow cabbage, without which we would have no kraut.

PEOPLE IN OUR PAST

In 1933, biochemist **Karl Paul Link** began an exhaustive search for the agent in spoiled sweet clover that was making cows bleed to death. Six years and countless bales of rotten clover hay later, Link found and synthesized dicumarol, a blood-thinning compound that would become an essential anticoagulant for treating blood clots. Later, after Link made more than 100 variants of dicumarol, the most potent blend became the basis for Warfarin, one of the most efficient rodent killers in history. Link's discovery saved thousands of human lives, killed millions of rodents and earned the university tens of millions of dollars.

FACULTY MEMORIES

In 1958 I enrolled in my first course in philosophy. The teacher was Professor Bagholt. He was most charismatic and charming, and was nearing the end of his career. On one occasion he argued at length about some philosophical issue, then asked if we were totally convinced that the proposition was correct. We all nodded in assent.

Then he proceeded to totally dismember the proposition and to convince us of the opposite point of view. We all left the class shaking our heads. Professor Bagholt opened my eyes to the power of critical thinking, and inspired me to take other Philosophy courses. His class always drew more attendees than those enrolled, and at the end of his last lecture he drew a sustained standing ovation.

— Harvey Malchow BS '61

TO GET INVOLVED

The Wisconsin Alumni Association is working with UW-Madison Archives to collect campus memorabilia of historical interest and value. If you have something of interest, please contact WAA, 650 North Lake St., Madison, WI 53706-1476; phone 262-2551 e-mail waa@badger.alumni.wisc.edu

For more on lecture series, see; Lectures-Link



From the University of Wisconsin-Madison / News Service, Bascom Hall, 500 Lincoln Drive, Madison 53706 / Telephone: 608/262-3571

Release: Immediately

6/1/82 jmn

CONTACT: Dean Robert M. Bock (608) 262-1044 or Robert Kimbrough (608) 263-3820

SPEAKERS TO BE NOMINATED FOR LINK LECTURES

MADISON--A University of Wisconsin-Madison committee will be appointed to nominate speakers for the new Elizabeth and Karl Paul Link lectureship.

Lectures are expected to be on scientific and humanitarian topics, according to graduate school Dean Robert M. Bock. It is hoped that enough funds can be raised to make the lecture an annual event, he said.

One of the UW-Madison's most distinguished professors, Karl Paul Link discovered the blood anti-coagulant drug Dicoumarin, which saved thousands of lives worldwide. Subsequently, he created the safest and most effective rat poison ever developed, Warfarin. An outspoken and sometimes controversial figure, Link promoted individuals' civil liberties and advocated freedom for students to speak out on political issues. He died in 1978.

His wife, Elizabeth, was a long-time member of the Society of Friends before her death April 24. She was known for her work in causes furthering peace and social equality. A recent memorial service (May 30) dedicated her home for world peace purposes.

Members of the lectureship committee will be named by Chancellor Irving Shain.

University of Wisconsin MADISON, WISCONSIN 53706

DEPARTMENT OF ENGLISH HELEN C. WHITE HALL 600 NORTH PARK STREET

7 May 1982

Robert M. Bock
Dean, the Graduate School
Bascom Hall

Dear Dean Bock:

This is the written follow-up to the conversation you had with the Elders and me on Wednesday, 28 April.

We should like your approval and endorsement of the formation of a committee to arrange an Annual Elizabeth and Karl Paul Link Lecture.

Karl Paul Link, accomplished scientist and champion of individuals' civil liberties, and Elizabeth Link, staunch advocate of peace and freedom in all communities, small and large, should be honored by the University of Wisconsin and the Madison community because of his countless intellectual, idealistic, and material contributions to the well-being and reputation of his university, and because of her untiring efforts in behalf of individual and social equity and justice in Madison and beyond. An appropriate vehicle would be an annual lecture open to the entire community by some distinguished scientist-humanitarian sympathetic to the Links' goals, in the lab and in life.

In order to insure that the initial aims of the lecture be kept in sight through ensuing years, a lecture committee which represents a broad range of the university should be constituted to select annually an appropriate speaker. For the present, allow me to suggest the following initial, interim make-up:

Joseph Elder, Sociology
Joseph Elder, Asian Studies
Robert Kimbrough, English
Robert March, Physics
Cretchen Schaff, General Engineering

Letter to Robert M. Bock 7 May 1982 Page 2

Ex Officio:
Dean of the Graduate School
Chair, Biochemistry
President, Madison Chapter,
Women's International
League for Peace and Freedom
One of the Link's sons, Paul or Tom

At present there is \$10,000 in the Wisconsin Foundation which should be authorized for the purpose outlined above, and, should this idea be approved and endorsed, we could raise further funds in connection with the memorial service to held for Elizabeth Link on May 30th.

Respectfully suggested,

Robert Kimbrough for the committee

RK:sm

cc: Robert Rennebohm
Peter Bunn
Thomas Link
Paul Link
The Link Estate
All named persons

THE GRADUATE SCHOOL UNIVERSITY OF WISCONSIN-MADISON

BAŞCOM HALL MADISON, WISCONSIN 53706

April 29, 1982

Dear Colleagues:

Students, colleagues, friends and family of Professor Karl Paul Link have given donations to establish a memorial fund in his name. Sufficient funds have been collected that the first Karl Paul Link dissertation year fellowship may now be awarded.

The solicitation for these funds stated that the Graduate School will consider nominations of any dissertation year student "whose area of study is concerned with the applications of scientific research in the evolution and encouragement of a peaceful and just international order."

In order to actively seek the best nominations from as broad an eligible cohort as possible, I am asking the advice of faculty members with experience in the problems and opportunities of many cultures and of applications of science to their internal and external problems. Nutrition, health, energy, communication, human rights, cultural awareness and understanding among cultures all have important relations with the application of science.

I ask that each of you actively seek out appropriate nominations of students for the Karl Paul Link fellowship. Please suggest to me the names of faculty likely to advise graduate research in the area of concern. There may be as much to gain from the awareness and support of a community of concerned scholars as from the actual support of a deserving student. If several nominations are received by June 15, 1982 a selection could be made for academic year 1982-3. If the nominations are slow in arriving, the selection would be made later in the fall semester of 1982-3.

Thank you for your help.

Sincerely,

Robert M. Bock

Dean

RMB:rm Attachment

Faculty Nominating Committee

Prof. Stefan S. Winkler, History of Medicine

Prof. Paul S. Boyer, History

Prof. James F. Crow, Genetics

Prof. Van R. Potter, Oncology

Prof. Seymour Abrahamson, Zoology

Prof. Edward E. Daub, General Engineering

Prof. Elizabeth A. Howe, Urban & Regional Planning

Prof. Jane A. Piliavan, Sociology

Prof. Robert Kimbrough, English

Prof. Peter P. Dorner, Agricultural Economics

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THE GRADUATE SCHOOL UNIVERSITY OF WISCONSIN-MADISON

BASCOM HALL MADISON, WISCONSIN 53706

ANNOUNCEMENT

Call for Nominations for the Karl Paul Link Fellowship:

Students, colleagues, friends and family of Professor Karl Paul Link have given donations to establish a memorial fund in his name. Sufficient funds have been collected that the first Karl Paul Link dissertation year fellowship may now be awarded.

The solicitation for these funds stated that the Graduate School will consider nominations of any dissertation year student "whose area of study is concerned with the applications of scientific research in the evolution and encouragement of a peaceful and just international order."

The Graduate Records of dissertation year graduate students are available and need not be enclosed. The nomination should describe the thesis topic and state why it is appropriate for this award. The nomination should list outstanding achievements of the student in scholarly activity and leadership. The date that preliminary examinations were taken or are scheduled should be listed. Forward the completed nomination to the Graduate School Fellowship Office, 217 Bascom Hall.

File Foln Acot

UNIVERSITY OF WISCONSIN-MADISON

COLLEGE OF AGRICULTURAL AND LIFE SCIENCES

Department of Biochemistry 420 Henry Mall Madison, Wisconsin 53706 USA Telephone: 608/262-3026/262-3040



May 1, 1979

A Memorial Service for Karl Paul Link, who died on November 21, 1978, will be held on Sunday, May 27, at 4:00 p.m. at the First Unitarian Society, 900 University Bay Drive in Madison.

Many of you have asked if there was to be a Memorial Fund in Karl Paul Link's name. We wish to inform you that a Dissertation-Year Fellowship is being established within the Graduate School, open to any student whose area of study is concerned with the applications of scientific research in the evolution and encouragement of a peaceful and just international order. Tax deductible contributions may be made to the Karl Paul Link Fellowship and sent to the University of Wisconsin Graduate School, c/o Dean Robert M. Bock, Madison, WI 53706.

Those of you who knew Karl Paul Link, worked with him, were aware how deeply committed he was to the concept of science as a great and beneficent instrument for improving the lives of humankind. He spoke often of his refusal to participate in what he felt were destructive uses of science. We, therefore, feel it fitting recognition of the principles by which he lived to embody those things he valued deeply in a University Fellowship.

The family has requested that flowers be omitted.

Professor and Chairman

Department of Biochemistry

Elizabeth F. Link



DAILY CARDINAL

From The University of Wisconsin-Madison / University News and Publications Service, Bascom Hall, Madison 53706 / Telephone: (608) 262-3571

Release:

LINK, Karl Paul

Link, the scientist as radical

P. 9, Part II--Summer Sessions '73 Registration Issue

NEWS OF THE UNIVERSITY OF WISCONSIN

From University Relations, 1752 Van Hise Hall, Madison 53706

Release:

Immediately

10/8/71 ca

(With Budget)

EMERITUS DESIGNATIONS

MADISON, Wis.--University of Wisconsin regents voted emeritus status for 28 professors Friday, 20 at UW-Madison, four at UW-Milwaukee, two at UW-Parkside and two in UW-Extension.

Madison faculty honored included Karl Paul Link, biochemistry; Richard V. Campbell, law; D.C. Smith, agronomy; Emory M. Pittenger, agricultural library; Harold G. Fraine, business; John W.M. Rothney, counseling and guidance; Henry Van Engen, mathematics and curriculum and instruction; J. Kenneth Little, educational administration; Kurt F. Wendt (also Dean Emeritus), administration and engineering mechanics;

E. Lida Kirchberger, German; Myron P. Backus, botany; James L. McCamy, political science; Henry A. Pochmann, Ednah S. Thomas, both English; Ovid O. Meyer, medicine; Charles V. Seastone, medical microbiology; Florence G. Blake, pediatric nursing; C. Evelyn Schmidt, nursing; Arthur H. Uhl (also Dean Emeritus), pharmacy; and S. Lee Burns, residence halls.

UW-Milwaukee's emeritus designations were voted to Edward Holst, English; Raymond Myers, communication; Theodore A. Rouse, physics; and Glenn Riddle, philosophy.

Two UW-Parkside assistant professors with tenure in the humanities, Henry L. Mann and Bernard P. Porzak, were named assistant professors emeritus.

UW-Extension faculty granted emeritus status were Prof. Oscar G. Woelfel and Assoc. Prof. Milo V. Johansen, both in community affairs.

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feature story

From The University of Wisconsin News and Publications Service, Bascom Hall, Madison 53706 • Telephone: (608) 262-3571

Release:

Immediately

5/17/71

(RETIREMENT SERIES)

By DOUGLAS D. SORENSON

MADISON--One of the University of Wisconsin's most/distinguished, most colorful professors will retire June 30. He is (Karl Paul Link) who discovered the blood-thinning drug Dicoumarin and the rat-killer Warfarin.

His discovery and synthesis of the anti-clotting material was announced in 1941 eight years after laboratory work had begun in the Madison campus department of biochemistry. The search started because a Wisconsin farmer's cows were dying, apparently from eating spoiled sweet clover hay. Some substance in the hay caused the blood to lose its clotting ability and the animals bled to death. Isolation of the substance gave medical science an anticoagulant drug that has saved thousands of human lives.

Seven years later, Prof. Link announced a derivative of Dicoumarin which killed rats by causing them to bleed to death. Patented and produced by the Wisconsin Alumni Research Foundation, Link coined the name Warfarin for the compound which became a nationally acclaimed safe, effective rodenticide.

The story of Karl Paul Link began Jan. 31, 1901, in LaPorte, Ind., where he was born into the family of a German Lutheran minister. He received a UW B.S. degree in agriculture in 1922, a year later an M.S., and in 1925 a Ph.D. in agricultural chemistry.

He left Madison to study in Switzerland, Austria, and Scotland, but returned to his alma mater to become a faculty member in 1927.

There the long hours of research began that culminated in Dicoumarin and Warfarin.

Dr. Link shared his work and his rewards with his graduate students. Many of them have gone on to become famous biochemists in their own right. He is a dynamic teacher, lecturing during his career to all biochemistry majors and often coming up with surprises to illustrate his points.

He has shown his non-conformist personality beyond the lecture hall and the laboratory. An unorthodox dresser, he is often seen in plaid shirt, high shoes, and a lumberman's jacket. He is never without a notebook and pencil to keep a record of ideas that may come to him at any time, while riding on a bus, in a store, or in the laboratory.

His unorthodoxy goes beyond his clothing and his bushy white hair. He has never hesitated to stand up for his beliefs, even if they caused trouble for him. Prof. Link often has disagreed with colleagues, administrators, and politicians. His most recent resistance to the "establishment" was his refusal to be photographed for a University identification card in 1969.

He has been recognized around the world with numerous awards in science and medicine. He holds the Albert Lasker Award of the American Heart Association, the Cameron Prize of the University of Edinburgh, Scotland, and the Jessie Stevenson Kovalenko medal of the National Academy of Sciences.

1/12/68 rt

RELEASE

Immediately

LINK GRANT

MADISON, Wis. - Dr. Karl Paul Link, University of Wisconsin biochemist whose dicoumarol and Warfarin have saved countless lives of people and killed millions of rats, has set up a \$400 defense fund to help students who are in difficulties with the University or with the law because of their support of unpopular causes.

University Regents accepted the fund Friday, designated the Madison

Campus Administration to administer it, and provided that additional contributions

could be added to the fund.

Dr. Link, who often has been active in controversial movements himself, is best known for his work on anti-coagulants which prevent the clotting of blood in humans who are suffering from various diseases, and which--in slightly different form--cause fatal bleeding in rats.

By dedicating his patents on these discoveries to the Wisconsin Alumni Research Foundation, Dr. Link has been instrumental in the support of a broad range of other productive University research projects.

uw news

From The University of Wisconsin News and Publications Service, Bascom Hall, Madison 53706 • Telephone: (608) 262-3571

Release:

10/25/67 jb

MADISON--Dr. Karl Paul Link, one of the University of Wisconsin's leading biochemists, received the Jessie Stevenson Kovalenko medal of the National Academy of Sciences Tuesday night.

Dr. Link was cited for his discovery and application of coumarin anticoagulants, a major weapon used by medical science to prevent blood clotting in thrombosis and atherosclerosis. It has been estimated that his discovery helped reduce by one-third the deaths resulting from blood clots following heart attacks.

His other contributions to human welfare include discovery of Warfarin, a lethal rodenticide.

A member of the UW faculty for more than 40 years, Dr. Link was the eighth recipient of the Kovalenko medal, established by Prof. Michael S. Kovalenko, a member of the Swarthmore College faculty from 1927 to 1939, in memory of his wife.

Dr. Robert H. Burris, also of the UW department of biochemistry, accepted the medal on Dr. Link's behalf at the autumn meeting of the Academy in Ann Arbor, Mich.

Dr. Link, who holds B.S., M.S., and Ph.D. degrees from Wisconsin, received the Cameron award of the University of Edinburgh, Scotland, in 1952; the Albert Lasker award of the American Public Health Association in 1955; John Scott award of the City of Philadelphia in 1959; and the Lasker award of the American Heart Association in 1960. He was elected to the National Academy of Sciences in 1946.

U. W. NEWS

11/20/62 ifn

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

RELEASE:

Immedia tely

MADISON--Pupils in more than 20,000 U.S. schools are hearing this week of the research discoveries of three famous University of Wisconsin scientists, Stephen Babcock, Karl Paul Link, and Harry Steenbock.

Pictures of the three Wisconsin scientists appear in the Nov. 19 issue of News Map of the Week, published by a Chicago firm as a visual aid for schoolrooms. The issue features accomplishments of the nation's Land-Grant universities, including Wisconsin. The 100th anniversary of the Morrill Land-Grant Act is being observed this year.

Dr. Babcock's dozens of important contributions to the dairy industry included a test for butterfat content of milk. Dr. Link's discoveries include Dicumarol, first of the synthetic anti-coagulants; Warfarin, leading rodent poison; and Plasmylac for treatment of calf scours. Dr. Steenbock's contributions include irradiation of food and pharmaceuticals with Vitamin D, helping conquer rickets.

The map shows laboratory pictures of the three Wisconsin scientists and two others from Land-Grant institutions, Dr. Selman Waksman, of California and Rutgers, who won the Nobel Prize for his discovery of streptomycin, and Prof.

Joseph Tykociner, who made the first public demonstration of sound-on-film at the University of Illinois in 1922.

Sixty per cent of living U.S. Nobel Prize winners earned degrees at Land-Grant institutions, the publication points out.

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

RELEASE:

Immediately

By GENE RODGERS

MADISON, Wis. -- University of Wisconsin biochemist Karl Paul Link has announced that he and his students have solved the last puzzle concerning the chemical nature of warfarin, the famous drug developed in the Link laboratory 20 years ago.

The Wisconsin scientists have discovered the absolute configurations of the molecules of warfarin, which occur in two "mirror image" forms. Research with the anti-coagulant is now devoted to explaining the mysterious mechanism by which as a medicine it enables peoplé to control blood clotting and as a poisonous overdose it kills rats painlessly.

The recent discovery revealed which of the two mirror image molecules, or enantiomers, of warfarin was dextro-rotatory and which levo-rotatory; that is, which was "right" and which "left." Like gloves, they are almost exactly alike but differ somewhat in their action; a left glove, for example, will not fit a right hand. Common, or racemic, warfarin is a mixture of the two.

Link, together with students Bruce D. West, Seymour Preis, and Collin H. Schroeder, laboriously separated the two forms from the natural half-and-half mixture by combining it with quinidine, another chemical with mirror image properties. The resulting compounds had properties sufficiently different to facilitate their separation, and from them pure "right" and "left" warfarin were

Like all enantiomers, one form rotates polarized light to the right and the other rotates it to the left, hence the names dextro- and levo-rotatory. More significant, it was discovered that the levo-rotatory form is seven times more potent than the other. However, they did not know which form, that is which absolute configuration, corresponded to which properties.

This was discovered by using an organic acid whose absolute configuration was known to synthesize an alcohol from which the levo-rotatory warfarin can be made. The absolute configuration of the warfarin was thereby inferred from the known structure of the acid.

It is hoped that that this new knowledge will and the studies of the physiology of warfarin; the structure of a molecule is often more important than its formula in determining its physiological activity.

It is known that warfarin goes to the liver and somehow interferes with the process of manufacturing prothrombin that occurs there, but the exact mechanism is unknown. Prothrombin is a protein necessary for blood clotting.

The Wisconsin scientists are now studying the intermediary metabolism of ingested warfarin, that is, what chemicals the body makes out of it, where they go, and how long they last. This is being done by using a Geiger counter to trace the path of radioactive warfarin through the bodies of rats,

Commenting on the success that he and his groups have enjoyed, Prof. Link said, "The secret is that my students never ceased to wonder, they kept on trying, and they were on a project directed toward doing mankind some good instead of trying to destroy it."

From: American Heart Association Kiel Auditorium Main 1-1964

For Release: PM's Saturday, October 22 and thereafter

Association for distinguished achievement in the field of cardiovascular research is presented jointly to three scientists for their pioneer work in the development and use of life-saving anticoagulant drugs. The awards were presented at the Association's scientific sessions here by Dr. A. Carlton Ernstene of Cleveland, President of the American Heart Association (left) to Drs. Irving S. Wright, New York, Edgar V. Allen, Rochester, Minn., and Karl Paul Link, Madison, Wisc. Each received an honorarium of \$2500, a statuette of the Winged Victory of Samothrace and an illuminated scroll.



GRAMERCY T.9170
FILE



MERICAN HEART ASSOCIATION, INC.

44 EAST 23RD STREET, NEW YORK 10

October 31, 1960

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Public Information Department University of Wisconsin Madison, Wisconsin

Gentlemen:

JM:bk

Enclosed herewith is a picture of Dr. Karl Paul Link receiving the 1960 Albert Lasker Award of the American Heart Association for your files or for use in publicizing the event.

Sincerely yours,

James McGraw

Public Information

Department

Supplementary Notes for some talk on

The Art and Science in the Development of Dicumarol (R), etc.

(Mostly Unpublished)

by

KARL PAUL LINK
(a professor)*

upon the occasion of the

U. W. Medical School Field Day April 29, 1960 (Class of 1960)

The place - Same hall where the first public lecture on Dicumarol (R) was given February 27, 1941.

^{* &}quot;Ein Professor ist ein Mensch der anderer Meining ist." from Fliegende Blätter.

Definitions of the scientific, neo-semi - or pseudo-scientific type.

Hackh's Chemical Dictionary - 3rd edition, Blakiston, Philadelphia, 1944 reads as follows on -

Page 814 - <u>substance</u>. A particular kind of matter. The material of which a body is composed: as a chemical compound or mixture of compounds.

ibid Page 218 - compound. A substance whose molecules consist of unlike atoms, and whose constituents cannot be separated by physical means. A compound differs from a physical mixture by reason of the definite proportions of the constituent elements (a proportion which depends upon their atomic weights) by disappearance of the properties of the constituent elements and the appearance of entirely new properties characteristic of the compound.

Thus glucose (blood sugar) or sucrose (cane or beet sugar) are compounds. Acetylsalicylic acid (pure aspirin) is a substance; likewise, Dicumarol (R) and/or warfarin sodium.

In contrast, heparin (a natural anticoagulant) is a <u>substance</u> - a biological - best assayed via its capacity to retard the clotting power of mammalian blood. There is no agreement on the "heparin molecule" - what it is, or how, chemically speaking, to assay its potency. But, it is useful in the clinic and elsewhere.

Webster's Collegiate Dictionary - 3rd edition, G&C Merriam Co., Springfield, Mass., 1929, reads as follows on -

Page 953 - stuff (OF estoffe) 1. Material out of which anything is to be or may be formed: hence, any material regarded indefinitely (v.t. 1 to fill by crowding; cram. 2. Specif.: To fill the cavity of (as a turkey, bedtick, or skin) with a particular material. 3. To crowd or fill with thoughts, ideas, etc., as to stuff one with lies. 4. To put fraudulent votes into (a ballot box) v.i. To feed gluttonously: cram. Stuffiness n. State or quality of being stuffy.

"PROTHROMBIN" is that ensemble or collection of gamma globulins involved in the coagulation of mammalian blood, be it in a test tube of glass, silicone lined glass, quartz or transparent plastic, etc.

Reference: see CIRCULATION 29, 97-107, 1959, January issue - specifically bottom page 99 column right.

3,

"THROMBOPLASTIN" is that collection of <u>stuff</u> from mammalian platelets, brain tissue, bone marrow and the like, etc. - involved among other things in blood coagulation.

"THROMBIN" is that stuff formed in step I of the blood coagulation phenomenon per below,

<u>"FIBRINOGEN"</u> is that protein complex in mammalian blood as defined by the late Professor Edwin J. Cohn (and subsequently by et al elsewhere) in <u>Blood and Blood Derivatives</u>, American Scientist 33, No. 2 page 61, 1945.

"FIBRIN" or "FIBRIN CLOT" is that stuff (or body of stuffs) formed at the tail end of the blood coagulation phenomenon inside or outside the body. In the body it can be new (freshly formed) partially aged or aged with or without infiltrations. It can contain any or all of the so-called 'organized bodies' of mammalian blood - be white or red in color, or grayish white, crimsoned somewhat, be in various stages of physical organization and/or disorganization - partially or substantially changed by the ferments of the body - be the body alive or dead. If you have never seen a "fibrin clot", go to the autopsy room.

Blood Coagulation Scheme (the classical one by MORAWITZ, FULD and SPIRO - modernized by the "ears")

Reaction 1

"PROTHROMBIN" + ionic Ca,* + "THROMBOPLASTIN" → "THROMBIN"

Reaction II

"THROMBIN" + "FIBRINGEN" → "FIBRIN" or "F-CLOT"

* possibly also any of the alkaline earths (as defined by Professor DMITRI IVANOVITCH MENDELYEEV (1834-1907) a Russian chemist, noted as one of the clearest formulators of the periodic law of the elements) from Group II could be involved, namely Be, Mg, Ca, Zn, Sr, Cd, Ba, Hg and Ra. Group II also now includes the isotopes such as SR 90, etc., as defined by the late FREDERICK SODDY F. R. S. (1877-1956). Professor Soddy was trained as a chemist. He taught chemistry. He did research in chemistry. He was Prix Nobel in Chemistry 1921. Soddy is frequently incorrectly referred to as a PHYSICIST by such "supreme" writers of current science fiction as Mr. William L. Laurence (and/or the like), New York Times, News of the Week, etc. See The Story of Atomic Energy by F. Soddy, London. Nova Atlantis, 1949.

The word <u>Nature</u> will also be used. See <u>A Short History of Medicine</u> by Professor E. H. Ackerknecht, M. D. Ronald Press. New York, 1955, (dedicated to William S. Middleton, M. D., the clinician, the medical historian and the man). Professor E. H. A. was once here -: he is now in Zürich, Switzerland.

See also Professor Charles Singer's book - same title. Oxford University Press, 1944. I now quote Professor Singer (last chapter):-

"To control Nature we must above all things understand Nature. Neither the conception of Nature as the kind old nurse nor the conception of Nature ravening red in tooth and claw will stand. Least of all can we tolerate the picture of Nature as a bountiful mother. If we go to her asking something for nothing, she (far from bountiful) will give us little but what we have given her, and to him who but begs she gives no more than a beggar's portion. It is thus that she has served the magician and the wizard, who think they can compel her to give them all things by their paltry charms!"

Lord Rutherford (1871-1937) said in his last lecture: "It is characteristic of science that discoveries are rarely made except when people's minds are ready for them." See <u>THE HISTORY OF RADIOACTIVITY</u> in <u>Background to Modern Science</u>. The University Press, Cambridge, England, 1940, page 55.

An aphorism by Francis Bacon (1561-1626) has often been verified in history. "Truth to emerge sooner from error than from confusion."

Apropros "Clinical Judgement":- "Life is short and Art is long: The Crisis is fleeting: Experiment risky, Decision difficult." See Hippocratic Wisdom, by the late W. F. Petersen, M. D. Thomas, Springfield, Illinois, 1946. (The copy I have was loaned to me by Professor Hans H. Reese (M. D.) in the Spring of 1946, when I was serving my first residence under the CROSS OF LORRAINE - across the lake. I always forget to return it).

The words of Hippocrates (born about 460 B.C.) presumably were recorded by some scribe. According to Celsus (about 178 A.D.) it was Hippocrates who first separated medicine from philosophy (talk). Hippocrates might well have had in mind thrombosis and thromboembolic complications when he dictated those words. See The Harvey Lecture Series. 39; 943, pages 162-216, specifically p. 208.

See also Johannes Müller (1801-1858) Handbuch der Physiologie des Menschen, 1833 -40. Translated into English by Dr. William Baly,

and published in London in 1842. I have in mind especially his Law of Specific nerve Energies or the Law of Specific Energy of Substances. Müller made numerous observations in various departments of physiology and in particular he extended knowledge as to the mechanism of voice, speech and hearing and as to the chemical and physical properties of lymph, chyle and blood.

See also C. Handbuch der Speziellen Pathologischen Anatomie und Histologie, Herz und Gefässe, Berlin, Springer, 2, 804, 1924.

See also Morawitz, P., Handbuch d. Inn. Med. (G. von Bergmann und R. Staelin) vol. 4, part I 1-306, Berlin, 1926.

See also Pickering, J. W. The Blood Plasma in Health and Disease. London, Macmillan, 1928.

The great Michael Faraday (1791-1867) wrote: "The philosopher (by this he meant scientist) should be a man willing to listen to every suggestion, but determined to judge for himself. He should not be biased by appearances; have no favorite hypothesis, be of no school, and in doctrine have no master. He should not be a respector of persons, but of "things". Truth should be his primary object. If to these qualities he added industry, he may indeed hope to walk within the veil of the Temple of Nature". Quoted in Introduction to Science, by J. Arthur Thompson. Thorton Butterworth Ltd., London, 2nd edition, p. 26, 1928.

FEATURE STORY

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN RELEASE:

By MACK LAING

MADISON--Two hundred and fifty University of Wisconsin medical students walked out of Service Memorial Institutes auditorium Friday to martial music from the opera Aida. The music signaled return of one of UW's most colorful lecturers to the public platform.

It was biochemistry professor Dr. Karl Paul Link--gesturing, wisecracking, philosophizing, heckling the audience--as guest speaker at UW Medical Center's Annual Field Day. The music was a pre-arranged flourish, an encore after the students' standing ovation.

It seemed a field day for Dr. Link as he started: "This is a day of triumph for me. This is my first public lecture since June, 1958." He explained that tuberculosis has kept him in Lakeview Sanatorium most of the time since then.

After a lengthy salute to the doctors who treated him, advice on how to ride Europe's Orient Express for second class fare in a first class seat, quotes from John Bunyan's "The Life and Death of Mr. Badman," Dr. Link assured his chuckling audience: "Well, the lecture's going to start pretty soon."

The subject was "Dicumarol, The Art and Science of Its Development." Dr. Link whisked through an illustrated talk on the anti-coagulant discovered in his laboratory in 1940, prefaced by the remark: "Dicumarol--that's common knowledge now. They even know about it in Boston."

Another Linkism: "I am by birth a sort of naive skeptic with a leaning toward the optimistic side."

Advice to the medical students: "You must ask nature questions. The right questions come only through sweat and tears. If you have never eaten your scientific bread with tears in your eyes, perhaps pinched by the fear that you are totally wrong, then I grieve for you."

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MADISON NEWS

4/27/60 db

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

RELEASE:

Immediately

MADISON--The annual University of Wisconsin Medical School Field Day will be held Friday, April 29, beginning at 9:30 a.m. in Service Memorial Institutes

Auditorium.

The field day, which consists of speeches and scientific exhibits, is held to stimulate student interest and participation in independent study and research.

Dr. Daniel Funkenstein, professor of psychiatry at Harvard University, will open the field day with a speech on "The Mastery of Stress."

His address will be followed by scientific exhibits at 10:15 a.m., a student-faculty luncheon at 12:30 p.m; and presentation of student awards at 2 p.m.

Prof. Karl Paul Link of the UW biochemistry department will speak at 2:30 p.m. on "Dicumarol, the Art and Science of Its Development."

The field day will close with athletic contests on the intramural fields at 3:30 p.m.

NEWS RELEASE

American Heart Association

44 EAST 23RD STREET, NEW YORK 10, N.Y. TELEPHONE: GRAMERCY 7-9170



FASE: PM's Saturday, October 22 and thereafter

Sa-6

LASKER AWARD OF AMERICAN HEART ASSOCIATION PRESENTED
TO THREE SCIENTISTS FOR WORK WITH ANTI-CLOTTING DRUGS

ST. LOUIS, October 22 -- The 1960 Albert Lasker Award of the American Heart Association was presented jointly today to Dr. Karl Paul Link, Madison, Wis., Dr. Irving S. Wright, New York, and Dr. Edgar V. Allen, Rochester, Minn., for their pioneer work in the development and use of life-saving anticoagulant drugs.

The award, given annually "for distinguished achievement in the field of cardiovascular research," was conferred on the three scientists during the Heart Association's Scientific Sessions which continue through tomorrow at Kiel Auditorium here. Dr. A. Carlton Ernstene, President of the American Heart Association and Chairman, Division of Medicine, Cleveland Clinic, presented the awards.

Anticoagulant drugs slow down the clotting time, thus preventing the formation of clots within the blood vessels which may block the circulation and cause heart attacks, strokes, and other cardiovascular disorders which together are the leading cause of death in the United States.

The investigators each received an honorarium of \$2,500, an illuminated scroll, and a gold statuette of the Winged Victory of Samothrace symbolizing victory over death and disease.

-more-

Lasker -2-

The award, one of the highest honors in American medicine, described the contributions of the scientists as follows:

Dr. Karl Paul Link

Karl Paul Link, Ph.D., Professor of Biochemistry at the University of Wisconsin, with his associates in 1939 discovered dicoumarin, the hemorrhagica agent fatal to cattle in spoiled clover hay. Later, he synthesized it as dicumarol, the first anticoagulant which could be administered orally. Dr. Link and his associates went on to the synthesis of other coumarin drugs which have helped save thousands afflicted with blood clotting diseases. His "persistent laboratory experiments despite many frustrations helped to open a new frontier for medicine through anticoagulant therapy," his citation points out.

Dr. Irving S. Wright

Dr. Wright, Professor of Clinical Medicine, Cornell University Medical College and former President of the American Heart Association, "played a vital role in encouraging the study and introducing the clinical use of anticoagulants, and in helping to establish proper safeguards and procedures," his citation states. He and his associates made medical history in 1938 as the first in the United States to treat a patient by intravenously administering the anticoagulant, heparin. He later advanced the clinical use of dicumarol through pioneering investigations with his associates and was among the first to use and advocate anticoagulants for the treatment of heart attacks and strokes. Dr. Wright is also noted for inaugurating and correlating a large-scale study which resulted in wide medical adoption of anti-coagulants for treatment of heart diseases.

Dr. Edgar V. Allen

Dr. Allen, Senior Consultant in Medicine at the Mayo Clinic and a past President of the American Heart Association, with his associates was among the first to confirm Dr. Link's laboratory studies of dicumarol and then to use it clinically. The first published report on the administration of this drug to humans was presented by Dr. Allen and his laboratory team in 1941. His citation notes that "by his leadership and encouraging example at the Mayo Clinic and through his reports before the country's eminent medical societies, he stimulated the dissemination of knowledge of this new therapy and gave impetus to the development of broader clinical studies."

The Lasker Award for cardiovascular research was established in 1953 by the Albert and Mary Lasker Foundation in cooperation with the American Heart Association. Previous recipients to date are: Dr. Paul Dudley White, Boston; Dr. Albert Szent-Gyorgyi, Woods Hole, Mass.; Dr. Carl J. Wiggers, Cleveland; Dr. Louis N. Katz, Chicago; Dr. Isaac Starr, Philadelphia; Dr. Irvine H. Page, Cleveland; and Dr. Robert E. Gross, Boston.

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CUT LINES

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

To: Saturday Evening Post

RELEASE: at will

12/7/59 jfn

DR. KARL PAUL LINK, professor of biochemistry at the University of Wisconsin, is famed for his discovery of dicumarol.

Dicumarol is a material which inhibits blood clotting and is credited with saving the lives of thousands of victims of heart ailments.

Pres. Eisenhower is perhaps the most famous recipient of the benefits of dicumarol. He has been taking the drug for several years.

For his dicumarol discovery, Dr. Link has received the coveted Lasker award and on Dec. 3, 1959, received the John Scott Award.

Another of his anticoagulants, Warfarin, also is a widely-used rat poison. Warfarin is a name coined by Dr. Link to include the initials of the Wisconsin Alumni Research Foundation. He has assigned most of his discoveries to WARF and they have yielded more than \$2 million to be used for research at the University.

Two pictures of Dr. Link are enclosed:

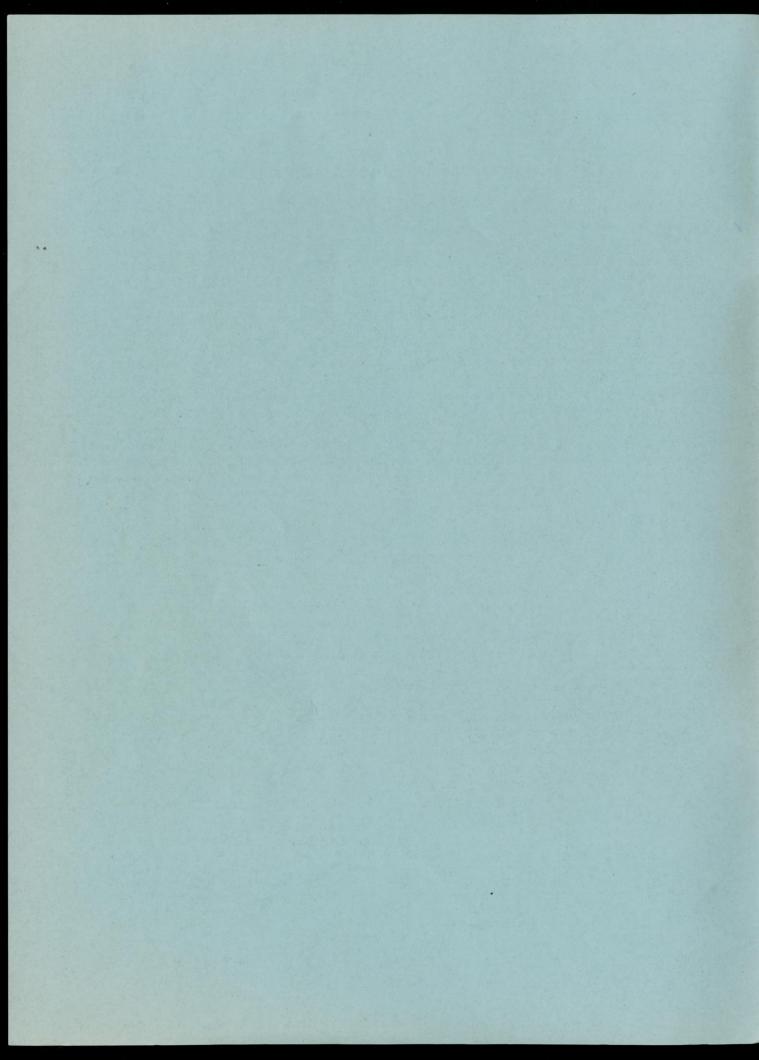
- (1) Lab shot with bottles of chemicals in background;
- (2) Head and shoulders portrait.

The Discovery of Dicumarol and Its Sequels

By KARL PAUL LINK, PH.D.

Comfined Carlinian (4/20/59

Reprinted from CIRCULATION Vol. XIX, No. 1, January, 1959 Printed in U.S.A.



The Discovery of Dicumarol and Its Sequels

By KARL PAUL LINK, PH.D.

THE STORY of Dicumarol* has been told several times by me in the past 17 years, and often by others. Like any good story it need not be told in exactly the same manner each time. In Wisconsin it has become a kind of legend. I shall consider only the high water marks of certain chapters.

Fortunately the basic scientific facts on the discovery and development have already been thoroughly recorded 1-6 so that little new information on Dicumarol and its sequels needs to be revealed here. However, when I do introduce new material it will be restricted to that which is documented or sustainable via memoranda or letters.

The story begins some 36 years ago on the prairies of North Dakota and in Alberta, Canada. In the 1920's a new malady of cattle involving fatal bleeding showed up almost simultaneously in these areas. The veterinarians, Schofield and Roderick, were forced to conclude that the cause of the disease was neither a pathogenic organism nor a nutritional deficiency. The origin of the new malady was traced to stacks of sweet clover hay mysteriously gone bad. Hence the disease became known in veterinary practice as "sweet clover disease" and it was found that it was caused only by improperly cured hay made from the common varieties of sweet clover. When first observed this disease was in a sense without parallel in animal pathology or human medicine. When cattle or sheep ate the spoiled hav the disease slowly became manifest by a progressive diminution in the clotting power of the blood (about 15 days) and resultant internal hemorrhage which usually became fatal in about 30 to 50 days.

From the Department of Biochemistry, University of Wisconsin, Madison, Wis.

It was recognized by Schofield and Roderick that the disease was reversible. It could be controlled in cattle by the withdrawal of the spoiled hay from the diet and by transfusion of blood freshly drawn from normal cattle, provided the hemorrhagic extravasation had not proceeded too far. Indeed, they showed that even in desperate cases, recovery could be hopefully anticipated after transfusion and change in diet (good hay).

In a comprehensive and thorough study of the pathology and physiology of the disease Roderick in 1931 emphasized that the delayed or abolished coagulability of the blood was due to a "prothrombin" deficit. Indeed he showed that the severity of the hemorrhagic condition paralleled the reduction in "prothrombin content or activity." He did this by using the technic developed by that great American pioneer of blood coagulation, the late Professor W. H. Howell. Solutions of what was then called "prothrombin" prepared by precipitation of normal bovine plasma with Howell's acetone method when added to the "sweet clover blood" promoted coagulation. In contrast, preparations of "prothrombin" made in a parallel manner from "sweet clover blood" did not produce coagulation. The other constituents for the maintenance of normal coagulability known at that (fibrinogen, calcium, platelets, and inhibitory substance) appeared to be unaffected.

I first learned about the hemorrhagic sweet clover disease of cattle in December 1932 through the late Ross A. Gortner, who then

Given February 25, 1958 at the New York Academy of Medicine under the auspices of the Section of Medicine and the New York Heart Association, on the programme, "The Historical and Physiological Aspects of Anticoagulants."

^{*}Dicumarol is the trademark for 3,3'-methylenebis-(4-hydroxycoumarin). The anticoagulant was made available in 1940 and 1941 for clinical use by the cooperative efforts of the Wisconsin Alumni Research Foundation, Madison, Wis., the Abbott Laboratories, North Chicago, Ill., Eli Lilly and Company, Indianapolis, Ind., and E. R. Squibb and Company, New Brunswick, N. J. The official U.S.P. name is bishydroxycoumarin.

headed the Biochemistry Department of the University of Minnesota. He had offered me a post and I had come to St. Paul to consider it. Since the "sweet clover disease" was also a problem in Minnesota it was one of the projects open for study if I chose to accept. It was Gortner who supplied me with the original publications of Roderick. Some attempts had been made in Gortner's department to extract the hemorrhagic agent but they, like those of Roderick and others, had failed.

Curiously, the "official start of our work in January 1933 in cooperation with Professor R. A. Brink and W. K. Smith of our Genetics department was on a different aspect of the sweet clover problem. They sought to develop a strain of sweet clover suitable for Wisconsin climatic conditions low in, or free from, coumarin. Though coumarin smells sweet (the characteristic smell of new mown hay is due to its presence) it tastes bitter, and it was known that the bitter taste of green sweet clover plants, Melilotus alba and M. officianalis, paralleled the total coumarin content. In actual practice it was observable that cattle (or rabbits) would eat the less bitter plants first.

Tragedy out on the Farm

Quite apart from the "official" start concerned primarily with the palatability question my laboratory had a direct catalytic hit from agricultural practice.

Indeed on a Saturday afternoon in February 1933 following the first conferences with Brink, while a blizzard was howling and the mercury was hovering near zero, a farmer from the vicinity of Deer Park, Wisconsin, some 190 miles from Madison appeared with what the late Professor A. J. Carlson might have called "the evidence." Curiously the farmer's name was Ed Carlson. The hemorrhagic sweet clover disease of cattle was rampant on his farm. He had fed sweet clover hay for years previously without encountering any difficulties and he doubted the veterinarian's diagnosis. Accordingly he was advised to go to the Agricultural Experiment Station authorities to get the facts. The office of the State Veterinarian had closed and pure chance had brought him to the Biochemistry Building.

Farmer Carlson's multiple evidence was a dead heifer, a milk can containing blood completely destitute of clotting capacity, and about 100 pounds of spoiled sweet clover—the only hay he had to feed his cattle.

His account of the over-all course of the disease coincided perfectly with the classical "sweet clover poisoning" picture. Late in December he had lost 2 young heifers. In January 1 of his favorite old cows had developed a massive hematoma on a thigh and following a skin puncture fatal bleeding set in rapidly. Finally 2 young cows had died on Friday and the bull was oozing blood from the nose. So he took off for Madison in a blizzard.

I immediately had to tell farmer Carlson that we could do no more at this time than to recommend the teachings of Roderick and Schofield. He had to stop feeding that hay, and possibly transfuse those desperately sick cattle, if he wanted to save them. Eventually it might become possible to make some usable recommendations to avoid such disasters, but not now.

I can still see him take off for home about 4:00 p.m. Those 190 miles of drifted roads between our laboratory and his barn must have appeared to him like a treacherous and somber ocean.

I cannot take the time to tell all the details of this slice of the Dicumarol story, but I can assure you its impact on me was immense. I will relate a part of it exactly as I did in my first lecture on Dicumarol given at the Mayo Clinic on March 12, 1942.

When farmer Carlson came to see us, my senior student and old man Friday was Eugen Wilhelm Schoeffel, a volatile Schwabian who came to the U.S. in 1926 with a diploma in Agricultural Chemistry. After serving a 2-year apprenticeship in the Chicago Stock Yards he began to study with me in 1929. Schoeffel is interesting, energetic, and loyal. He was then and still is, somewhat of a mystic and inclined in ordinary conversation to quote freely from Goethe's Faust, Shakespeare, and the Bible, as well as other primary sources. In 1933 his spoken English was not only strongly guttural, but also very earthy, punctuated frequently with Schwabian German.

After farmer Carlson left, Schoeffel stormed back and forth in the laboratory shouting, "Vat da Hell, a farmer shtruggles nearly 200 miles in dis Sau-wetter, driven by a shpectre and den has to go home vit promises dat might come true in five, ten, fifteen years, maybe never. Who knows? 'Get some good hay—transfuse.' Ach!! Gott, how can you do dat ven you haf no money?'' he snarled.

He dipped his hands into the milk can repeatedly and while rubbing them muttered, "Dere's no clot in dat blook! BLUT, BLUT VERFLUCHTES BLUT. 'Die Menschen dauern mich in ihren Jammertagen.' " (Faust Prolog., line 297) and then, "Vat vill he find ven he gets home? Sicker cows. And ven he and his good voman go to church tomorrow and pray and pray and pray, vat vill dey haf on Monday? MORE DEAD COWS!! He has no udder hay to feed—he can't buy any. And if he loses de bull he loses his seed. Mein Gott!! Mein Gott!! Vy didn't ve anti-shi-pate dis? Ya, ve should haf anti-shi-pated dis."

We took the blood and hay and played about with them until about 7:00 p.m. when I headed for home. As I left the laboratory, Schoeffel grabbed me by the shoulders, looked me squarely in the face and said, "Before you go let me tell you something. Der is a deshtiny dat shapes our ends, it shapes our ends I tell you! I vill clean up and gif you a document on Monday morning."

Development of the Bioassay

Two fundamental issues confronted us. First there were no *chemical* criteria available to establish the presence of the hemorrhagic agent. Therefore, a *bioassay* involving a small experimental animal (rabbits)) offered the only practical means of appraising the anticoagulant activity of test hays and extracts prepared therefrom.

It was clear from the pioneer papers of Roderick that the sweet clover disease was completely reversible. The eating of spoiled hay, even over long periods, caused no permanent functional change, no demonstrable morphologic change, and no detectable pathologic change of the liver, the assumed primary site of prothrombin synthesis. Nevertheless,

the immediate prospects of developing a reliable and simple bioassay were not bright; indeed they were dark, "dark like the inside of a cow." We had not had previous experience with that complex problem—blood coagulation.

Schoeffel and Roberts first showed that the Howell method for estimating prothrombin activity did not have the precision required. Smith and Roberts showed that the whole blood coagulation time was too variable, and that the Quick 1-stage method using whole plasma left much to be desired. Smith also showed that there was a wide variation in the response of individual rabbits to the standard dose of 50 Gm. of the spoiled hay. So Campbell and Smith bred and reared a susceptible rabbit colony specifically for the assay.

At that time, 1935-1938, a bloody and amusing polemic raged among the coagulation specialists on how to estimate "prothrombin concentration or activity"-whether it should be done by the 1-stage method of Quick* or the 2-stage method of H. P. Smith and coworkers. 1-3, 8 We tried to keep out of that brawl. In 1938 Campbell finally got over the chief obstacles. He adapted the Quick 1-stage method to our conditions, primarily by relying on the clottability of diluted plasma within the concentration range 12.5 to 8.34 per cent. He eliminated some of the inherent daily variations by fasting the assay rabbit 24 to 36 hours before feeding any preparation under test, by making the plasma clottability tests promptly after drawing the blood, and by comparing the test plasma against the normal plasma of each rabbit.

Through the use of individually standardized rabbits (the standard response being that

^{*}The intricacies of the blood coagulation phenomenon are outside the scope of this discourse. Suffice it to state that it is now accepted by most "coagulationists" that a prolonged Quick 1-stage "prothrombin time" (when the fibrinogen is normal) induced by Dicumarol and the like is a primary deficiency in factor VII and prothrombin. See British Medical Bulletin, vol. II, no. 1, Blood Coagulation and Thrombosis, Medical Department, The British Council, London, November (1955), and the lectures by Owren P. A. on Coagulation of Blood, etc., Northwest Medicine, January, pp. 31-39, February, pp. 159-166, and March, pp. 298-307, 1957.

induced by the anticoagulant in 50 Gm. of spoiled hay) and by having the assay on a strictly differential basis the ever present problem of biologic variation was greatly reduced.

Some side observations were made by Campbell on the plasma of rabbits fed the spoiled hay or fractions thereof that were later reported by others. A plasma factor beyond that needed by the classical blood coagulation expression of Morawitz-Field and Spero was hinted at in one of Campbell's reports. But these hares were not hunted. Our goal was to make real a substance that abolished the clottability of cattle blood in agricultural practice. To use the vernacular, the bioassay using the 1-stage plasma clottability was altered so that "it worked," and few of the valuable assay rabbits were lost in the process. One of them known as Bess Campbell was used for about 200 individual assays, over a period of 5 years.

Isolation, Crystallization, Identification, and Synthesis of Dicumarol

Between that fateful Saturday in February 1933 and June 1939 a long and arduous trail was followed by Smith, Roberts, and especially Campbell, to lay the anticoagulant out on the bench. I would like to detail some of the chemical extraction, separation, and isolation problems that the spoiled sweet clover hay presented. This hay was indeed a kind of biochemical grab-bag and yielded many inactive products, some new, most of them old. But suffice it to state that many a seething and simmering hope did not become reality. At times the hemorrhagic agent appeared to hover before us like thistle down only to elude us like the will-o-the-wisp. At one time it was thought to be a porphyrin-like substance, a pheophytin resulting from the degradation of the chlorophyll in the spoiling process.

Finally in the dimness of dawn on June 28, 1939, after working all night, Campbell saw on a microscope slide what turned out to be crystalline Dicumarol. Two hours later he had collected about 6.0 mg. of it.

When I reached the laboratory that morning Campbell was asleep on the laboratory couch; the door to the room was guarded by one Chet Boyles, a soldier of fortune on the W.P.A. relief roles, who assisted Campbell with the bioassays. Boyles was an excellent handler of animals for he had served 2 years as helper to a veterinarian before he came to us.

As I walked into the room, Boyles was taking a nip from the contents of a bottle whose bottom layer consisted of carpet tacks, the upper layer of 95 per cent ethanol. Without the flicker of an eyelash Boyles said to me, "I'm celebrating, Doc. Campy has hit the jack-pot." (As though I didn't know that he had been hitting that bottle for months.)

But Boyles' surmise was correct this time. Campbell did have Dicumarol and the first bioassay to establish its anticoagulant potency was already in process!

Campbell avoided me for 2 days—until the results of the assay were available—and then he came in to report.

There is a bed-rock of matter-of-fact common sense in Campbell's makeup. He was not inclined to show his emotions, but it was apparent that he was secretly as happy as a boy who had just caught his first big fish. He passed the vial to me and said, "This is H. A.!" (H. A. was the laboratory code for hemorrhagic agent.) I did not disclose that Boyles had given me the tip-off. I told Campbell that I knew a couple of lines of German poetry that fitted the occasion, and I recited to him,

"So halt'ich's endlich denn in meinem Händen

Und nenn' es in gwissen Sinne mein."

We sent a short wire to Schoeffel, who was then in the control laboratory of the American Medical Association in Chicago. He responded at once with a 200-word reply wherein he expressed his *complete* confidence in Nature, Fate, and us.

Mass isolation was started at once, and a stock of about 1,800 mg. of the crystalline anticoagulant was accumulated (Stahmann).

The problem of determining its structure fell to the sensitive, brilliant, and deft C. F. Huebner, who with some assistance from his lively imagination made the correct structural diagnosis as 3, 3'-methylenebis (4-hydroxycoumarin). He set the sights for the synthesis, which was achieved on April Fool's day, 1940. The synthetic and the natural product were shown to be chemically identical. Subsequently, Overman and Sullivan, through carefully conducted tests on the rabbit, rat, guinea pig, mouse, and dog, hall-marked the natural and synthetic products as biological equals.

The determination of the structure of the anticoagulant as a 3-substituted derivative of 4-hydroxycoumarin makes it appear that both of the undesirable aspects of the common sweet clovers—their unpalatability (bitterness) in the green state and the tendency of the hays to cause hemorrhage when improperly cured—have a common basis in the coumarin molecule. The biological synthesis during spoilage can be rationalized as an oxidation of coumarin to 4-hydroxycoumarin which upon coupling with formaldehyde leads to Dicumarol.

Physiologic Action of Dicumarol

After synthetic Dicumarol became available in quantity the essentials of its physiologic action were quickly established. It was shown that there is a lag in response, a variation in the intensity and duration of the hypoprothrombinemia (plasma prothrombin clotting time), depending on the size of the dose. In each species tested a certain single dose level gives the most efficient response. Below this level the efficiency of action is decreased by a threshold effect and at high levels by incomplete absorption of the drug.

Due to the latent or lag period of 12 to 24 hours before the drug's action becomes apparent, there is a cumulative effect following repeated administration. Thus it was anticipated that in clinical practice this action will

vary with the individual and because of this variation optimal therapeutic effects without hemorrhage would be obtained only when the dosage is individualized.

A brief summary 1-3 of the details follows:

- 1. There is a wide species difference in the response induced in the rabbit, rat, guinea pig, mouse, dog, cat, and chicken, and this varies with the age and sensitivity of each individual. Broadly speaking, the rat and mouse are the most sensitive, the cat and dog intermediate, and the rabbit, the cow, and the chicken the least sensitive.
- 2. The vitamin K and C levels in the diet affect not only the intensity but also the duration of the anticoagulant action. I propose to elaborate on this later.
- 3. The nutritional status of the animal affects the anticoagulant response—fasting generally enhances it in all species.
- 4. Any pre-existing hypoprothrombinemia like that inducible by the salicylates (aspirin), the sulfa drugs, or mild chloroform anesthesia augmented the response.
- 5. The hepatic and renal function influences both the intensity and duration of the response.
- 6. The presence of drugs that affect the total functioning capacity of the liver, like the methylxanthines (theophyllin) and the digitalis drugs, have a mild but definitely detectable counter action.
- 7. Pregnant or lactating females show a slight resistance to the drug's anticoagulant action.

These observations did not exhaust the conditions that can influence Dicumarol's action but they cover the essential points. Finally, it should be added that in Dr. Best's department at Toronto, Dale and Jaques first⁹ and later Meyer and co-workers¹⁰ at Wisconsin General Hospital, and others^{11–13} were able to show that a primary relationship exists between thrombus formation and the clotting mechanism of the blood. These studies established for the first time that an effective reduction of extravascular and intravascular thrombus formation parallels the diminished hypocoagulability induced by Dicumarol. It

was also shown by Spooner and Meyer¹⁴ that, when Dicumarol is given to dogs in safely usable therapeutic doses, it definitely decreases platelet adhesiveness; at the same time Quick showed that it also reduced platelet agglutinability.¹⁵ Thus the clinical use of the anticoagulant as a prophylactic agent for (against) thrombosis rested on a sound experimental basis.

Breaking the Bonds of the Usual Pattern of Thought

When we turned Dicumarol over to the clinicians in the years 1940 to 1942, one significant point, clearly established by our work, was at first missed, in fact denied.⁶ I have reference to the capital fact that vitamin K (all forms-some better than others) can counteract the action of Dicumarol.* I emphasized this in letters, personal conversations, and in my first lecture on Dicumarol at the Mayo Clinic and at Wisconsin General Hospital. In spite of these efforts the first clinical reports carried the statement that "vitamin K has no effect as an antidote to the administration of Dicumarol." The editorial and annotation writers for the medical journals, those who only "think" but "don't try," innocently reiterated this statement.1, 2 While in error, the clinicians were in good company, for an authority on blood coagulation16 had written in 1937, and again in his book published in 1942, that "vitamin K will not restore the prothrombin concentration" depleted by Dicumarol.17

Originally these denials made me very unhappy. The misfortune of being accused of error was not the primary basis for the unhap-

Normal bull Spoiled sweet clover hay Vitamin
$$K_1$$
 concentrate Bleeding bull

a completely reversible reaction,

piness, for we were certain that the antidotal capacity of vitamin K would in time be sustained in the clinic. What did disturb me was the needless induction of the hemorrhagic "sweet clover disease" in man and the stigma temporarily attached to Dicumarol, that it was a dangerous drug. And this did happen.

A feature of science that has always appealed to me is that sooner or later, and usually sooner, "the truth will conquer."

Dr. Shepard Shapiro in New York City was the first clinician (February 1942) to sustain our claims that vitamin K can counteract the anticoagulant action of Dicumarol in man when liver function is adequate.^{5, 20} Subsequently he was independently supported by Townsend and Mills in Canada,²¹ Lehman in Sweden,²² and finally by Cromer and Barker²³ at the Mayo Clinic, as well as others. Today it is accepted that the water-soluble forms of vitamin K or vitamin K₁ given orally can successfully antidote overdosing with Dicumarol, provided they be employed when reversal is still possible.

Let us briefly examine why the error arose. The clinicians did not use a 1-stage prothrombin assay as sensitive as the one Campbell developed for our experimental animals. They were originally conditioned to the low levels of vitamin K effective in obstructive jaundice, biliary fistula, cholemic bleeding, etc. It was also thought that the menadione form of vitamin K might be toxic. Over 10 years were required to wipe out this error from clinical practice.

To summarize, surmise, faulty thinking, and not enough trying kept vitamin K from being the corner building stone in Dicumarol therapy that it deserved to be from the outset.

In 1950 Marple and Wright (pages 149 and 181)⁶ wrote, "When bleeding occurred from the clinical use of Dicumarol the fault rested with the physician who administered the drug."

Enthusiasm-Muddle-Consolidation

Within 2 years after Dicumarol was synthesized, over 100 related 3-substituted 4-hydroxycoumarins were prepared in my lab-

^{*}For an account of how, in January 1939, a bull desperately sick from eating spoiled sweet clover hay (he was ''down,'' blood was oozing from the nose, and a massive hematoma adorned the right thigh) was rescued from the clutches of death via a vitamin K_1 concentrate prepared from alfalfa hay, see reference 2. Originally not even this ''bull story'' could break the bonds of the usual pattern of thought. The equation is

oratory. Synthesis ran substantially ahead of biochemical appraisal. Accordingly, when I gave the Harvey Society lecture on "The Anticoagulant from Spoiled Sweet Clover Hay" in January 19441 it was indicated that "it would not be valid to conclude from the relative appraisals on activity made with the rabbit-that Dicumarol is the most desirable compound for clinical use." It was indicated that "In the course of the routine appraisal of the many compounds tested it was learned that some of them exhibited a slower but more sustained hypoprothrombinemic action, while the action of others is of shorter duration. It will take some time before final judgment can be passed on this subject. From the experience gained with other pharmacological agents it is abundantly clear that the final test is the action in man under a variety of conditions. The unpredictable can be surprising, so, as we see it, we might now be at the beginning of things and not at the end in this field of study."

Being an agriculturist I have little confidence in predictions, including my own. The situation can now be appraised in the light of wisdom after the event. Bear in mind that the statement quoted was made less than 4 years after Dicumarol became known to us and before extensive clinical information on the response in man was available. About 50 reports on the clinical use of Dicumarol had appeared between 1941 to 1944.^{5, 6*}

The appearance of any new drug creates an interesting cycle of events, and Dicumarol went through that cycle quite rapidly. The first preliminary reports indicated that an atmosphere of optimism prevailed. They evoked

prompt favorable editorial comment in the Lancet (September 13, 1941) under the title, "Heparin and a Rival." Then came the second period—a period of muddle. Enthusiasts and skeptics for anticoagulant therapy with Dicumarol were created, and it can be stated that some of the skeptics condemned the drug in no uncertain terms, though they were largely armed with surmise, faulty, or no prothrombin clotting time determinations and they used the antidote vitamin K inadequately. Then came the third period of consolidation, from which it can now be concluded that a better anticoagulant of the Dicumarol type was desired.

Since Dr. Wright asked for aspects of human interest, let me add another slice from the Dicumarol story. Early in September 1945 I was fed up with laboratory work, etc., and I went off on a canoe trip with my family. On this trip we were caught in a cold rain storm. I got soaked and overexhausted. Two weeks later I came down with what I had had once before-after a similar heavy physical bout, as a student in Switzerland-wet pleurisy. At first my doctor thought I had pneumonia; then I told him about my previous bouts of tuberculosis; so the diagnosis was changed to reactivated pulmonary tuberculosis. I spent 2 months at Wisconsin General Hospital and then was transferred to Lakeview Sanatorium headed by the double cross of Lorraine. Here I was supposed to vegetate like a topped carrot. I did rest there, physically for 6 months, took nothing stronger than cod liver oil and 3 bottles of beer a day, but kept the aged tuberculosis out of my mind by studying laboratory records and reading the history of rodent control from ancient to modern times.24, 25

A "Janus" in the Coumarin Family

Now brace yourselves, for I propose to shift from a "cow poison" that had become a drug of substantial clinical usefulness, to a "rat poison" converted to a drug, which has I believe most of the desirable features that can be expected from an anticoagulant to be given primarily via the oral route.

^{*}The first clinical report to appear was by Butt, H. R., Allen, E. V., and Bollman, J. L.: Preparation from spoiled sweet clover (3,3'-methylene-bis-4-hydroxycoumarin) which prolongs the coagulation and prothrombin time of blood: Preliminary report of experimental and clinical studies, Proc. Staff Meet. Mayo Clinic 16: 388-395 (June 18), 1941. See also Allen, E. V., Barker, N. W., and Waugh, J. M., J.A.M.A. 120: 1009, 1942; Wright, I. S., and Prandoni, A., J.A.M.A. 120: 1015, 1942; Bingham, J. B., Meyer, O. O., and Pohle, F. J., Am. J. M. Sc. 202: 563, 1941.

The many coumarins synthesized between 1940 and 1944 were listed by numbers in logical groups based on their chemical structure. While I was in the sanatorium in 1945-1946 the laboratory work was practically at a standstill. There were few students available, since most of them were still in the armed forces. So I had ample time to reexamine all the chemical and bioassay data available. Upon the return of L. D. Scheel from service in the spring of 1946, he was assigned to the task of reappraising the anticoagulant activity of the compounds numbered from 40 to 65. They were made by Ikawa in 1942-43. Instead of using only rabbits for the bioassays Scheel also used rats, mice, and dogs. In 1946-1948 he defined coumarin numbers 42 and 63 as being much more potent than Dicumarol in the rat and dog, as capable of producing a more uniform anticoagulant response, and as having the quality of maintaining a more severe state of hypothrombinemia without inducing visible bleeding. Certain chemical properties were also considered: the degree of purity readily attainable (absence of taste and odor), the cost of making them, and the property of being convertible to stable water-soluble salts.

Back in 1940 to 1942, Overman, Field, and my colleague, C. A. Bauman, had studied extensively the action of Dicumarol in the laboratory rat, and the effect of diet on the response, specifically the influence of vitamin K and foods rich in it. Later in 1942 I personally, with the help of good old Schoeffel, set up field trials to ascertain the suitability of Dicumarol for rodenticidal purpose. It was concluded that the activity of Dicumarol in the rat was not high enough to make it practical for rodent control. This was found to be largely due to the vitamin K content of mature grains and the availability of green foods with a high vitamin K content. It was shown that rats could tolerate a daily intake of 2.0 mg. of Dicumarol for 60 or more days due to the vitamin K content of the natural foods available. On a semisynthetic diet essentially free from vitamin K the survival time was about 15 to 23 days. When 5 mg. of vitamin K per day were added to the artificial

diet, the rats also tolerated 2.0 mg. of Dicumarol daily for over 60 days.

Early in 1948 I told Scheel and Dorothy Wu that I wanted to propose no. 42 for rodenticidal use.24, 25 This proposal shook the laboratory. I can sum up by stating the consensus of opinion "the boss has really gone off the deep end this time." Scheel favored no. 63 for clinical purposes. They are chemically closely related, no. 63 being a direct derivative of no. 42. To make a long story very short, early in 1948 no. 42 was promoted for rodent control under the auspices of the Wisconsin Alumni Research Foundation through the able, enthusiastic, and publicspirited Ward Ross, General Manager of this organization. Within a short time this effort revolutionized the art of rodent control (multiple doses as opposed to the single dose of the highly toxic poisons), and warfarin rapidly became and still is the leader in the rodenticide field.* The name Warfarin was coined by me by combining the first letters of the Wisconsin Alumni Research Foundation with the "arin" from coumarin-and it is now a household word throughout the world.***

Between 1948 and 1952 Dicumarol was, so to speak, being squeezed by chemical kin stemming primarily from European studies.²⁶ "Imitation is the sincerest form of flattery." Curiously, one of them, a derivative of Dicumarol, trade-named Tromexan, was not seriously considered by us as early as 1940. Though it acted somewhat faster than Dicumarol, it required substantially larger doses

^{*}Just as cattle eat hemorrhagic sweet clover hay until they die without visible sensory responses, the rat eats warfarinized cereal grain bait until fatal hemorrhage sets in. Neither bait refusal nor bait shyness develops. Indeed, the rodent's departure is biblical "death without sting." In Maxwell Anderson's drama, Elizabeth the Queen says, "To the end of time it will be so . . . the rats inherit the earth." Since warfarin has become available, this need not be so. Furthermore, via the water-soluble warfarin sodium the rat can drink unto death.

^{**}Warfarin is the safest rodenticide known. Up to now, in the United States there is no recorded case of a warfarin-induced fatality in man, although over 140,000,000 pounds of warfarin containing bait (0.025 per cent) have been distributed since 1950.

to get the equivalent anticoagulant action.* The second, Marcumar, a close kin to warfarin, was also passed by us, since its water-soluble sodium salt is less stable than warfarin sodium. Milligram for milligram, Marcumar is more active than warfarin and its action is also more prolonged. But as a result of the claims made about Tromexan and Marcumar

*The clinical promotion of Tromexan (bis-3,3'4-oxycoumarinyl) ethyl acetate, referred to as B.O.E.A. in the article by Burt, C. C., Wright, H. P., and Kubik, M., Brit. M. J. 2: 1250, 1949, precipitated interesting editorial comment under the heading, Dangers of Dicumarol (pp. 1279-1280). In this editorial it was suggested that since Tromexan seemed to be superior to Dicumarol "owing to its shorterlived action . . ." and in view of recent reports of the drug's (Dicumarol's) efficiency as a rat poison, it may be that Dicumarol will ultimately be more useful for that purpose."

Unfortunately the significance of our paper on the action of Dicumarol in the rat dealing specifically with the effect of diet and vitamin K on the anti-coagulant action (J. Nutrition 23: 589-602, 1942) was not appreciated by O'Conner, J. A., Research 1: 334, 1948, who suggested the use of Dicumarol for rodent control. Had O'Conner read our paper carefully, he would not have made this suggestion. The critical issue is that Dicumarol's anticoagulant action in the rat subsisting on natural grain foods is too slow to be practical. The level of Dicumarol in the bait has to be set so high that other animals (cat, dog) and children (accidental ingestion) would be vulnerable.

It was the inefficiency and slowness of Dicumarol to kill rats under practical field conditions that caused me not to suggest its use as a rodenticide in 1941-1943 (letter, Link, K. P., to the National Defense Research Council, Washington, D.C., dated March 10, 1943, and confidential disclosures, 1942-1943, to the late Professor Homer Adkins and Professor H. Gilman, official investigators and project leaders of N.D.R.C. and O.S.R.D. (confirmatory letter of Gilman to Link, June 11, 1952). Instead of Dicumarol the much more potent and efficient (no. 42) warfarin was recommended. Nevertheless, O'Conner's paper served a useful purpose in rodenticide control circles, and he must be accredited with being the first one to stimulate, via the printed page, the backward pest control workers by pointing out the potentials of anticoagulants (Link, K. P., letter December 6, 1948, to U.S.D.I. Fish and Wildlife Service, Denver, Colo.). I had attempted to create an interest in warfarin via letters and memoranda, which at first failed to reach the objective (see reference 24 and particularly reference 25). A complete history of the warfarin development based on 10 years of practical field experience is in the process of being prepared.

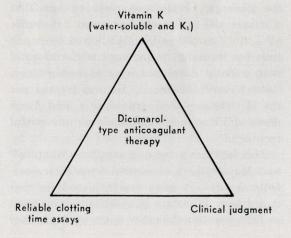
I took another good look at the mass data in the light of what clinicians were seeking, namely an anticoagulant that could be used via any route with the retention of the virtues of Dicumarol but without its limitations.

Based in part on the supposition that the response of the rat to warfarin (no. 42) was a very reliable index of how man would respond, late in 1950 I told Dr. S. Shapiro and Dr. O. O. Meyer that the water-soluble sodium salt of warfarin should be tried on man. In 1941 the clinicians had literally snatched the "cow poison" from us, but the transition to a substance originally promoted to exterminate rats and mice was a bit more than they could accept with real enthusiasm. Then, on April 5, 1951, we were informed by Captain J. Love (MC) in the U.S.N. at Philadelphia that an army inductee was admitted to the Naval Hospital who had taken over a period of 5 days a concentrate of warfarin designed for rodent control.²⁷ The package contained 567 mg. of warfarin in corn starch. The inductee had followed the multiple dose directions on the package. It became clear to him that warfarin was not an efficient agent "to shuffle off" this "mortal coil." It allowed too much time for thinking—so he went to the hospital with a fully developed case of hemorrhagic "sweet clover disease." He was treated per the directions-blood transfusion and large doses of Vitamin K-and made an uneventful recovery.28

This incident acted as a catalyst. Shapiro²⁹ and Meyer³¹ both concluded from their carefully done work with warfarin sodium that it did possess certain properties not inherent in Dicumarol or the other anticoagulants they

had tried. After Collin Schroeder perfected the process of making warfarin sodium, I induced my long-standing friend, Dr. S. M. Gordon, of the Endo Laboratories, Richmond Hill, N.Y., to make it available for clinical This he did, under the trade name Coumadin Sodium. Today it would appear, from the 15 to 20 clinical papers on warfarin sodium that have been published (see reference 32), that most of the drawbacks of Dicumarol have been overcome. Warfarin sodium is at least 5 and possibly 10 times more potent than Dicumarol. It is the only synthetic anticoagulant available today for therapeutic anticoagulation that can be given orally, intravenously, intramuscularly, or rectally.³² The rate of absorption is almost the same, irrespective of how it is administered. No other anticoagulant of the Dicumarol type has all these virtues. Of course, an overdosage can be readily corrected via vitamin K. It acts faster than Dicumarol, and fewer prothrombin times are required in its routine use. To use the words of both Shapiro and Meyer, "It is easier to handle clinically." It is my firm belief that in time it will replace Dicumarol on the basis of its performance over a wide variety of conditions and that other anticoagulants of the Dicumarol type will not be superior.

It always seems appropriate to me to visualize successful anticoagulant therapy with the Dicumarol-type drugs as being shaped like a triangle with accurate "prothrombin assays" at one corner, vitamin K at another, and sound clinical judgment at the third.



Each corner is linked to the other by way of the connecting sides. There should be no separation, each is vitally dependent on the other two. Though the clinical judgment be good and the "prothrombin time" accurate, the vitamin K corner might still have to be evoked, since each individual patient is essentially "an unstandardized biologic entity," errors in dosage can be made by the hospital service, the patient might have a silent ulcer, or the functioning of the *liver* or *kidney* might unknowingly be penumbral.

On September 29, 1955, I got a card from a former Wisconsinite working in Fitzsimons Army Hospital in Denver, Colorado which read, "The President is getting one of your drugs and it's not Dicumarol." A day later press secretary J. C. Hagerty announced,33 "The heparin which was used initially as the anticoagulant has been replaced by a drug of the Dicumarol type. The present prothrombin level has been well maintained." I knew of Colonel Pollock's paper, "Clinical experience with warfarin (coumadin sodium a new anticoagulant)," read before the first annual meeting of the American College of Angiology Atlantic City, N.J., on June 4, 1955, and I surmised that the most important man in the world today was being anticoagulated via warfarin sodium.34 This surmise proved to be correct and since then it is an open secret that warfarin sodium was being used. "The unpredictable can be surprising."

In closing I wish to indicate that what my laboratory has achieved in the past 2½ decades represents the combined effort of many students. It is fun to be the reporter or narrator of this highly successful adventure. To use the words of the late Allan Gregg, 35 my students represented much "emergent ability." I think the secret of their success is 3-pronged: they never ceased to wonder, they kept on trying, and they were on a project directed toward doing mankind some good instead of trying to destroy it.

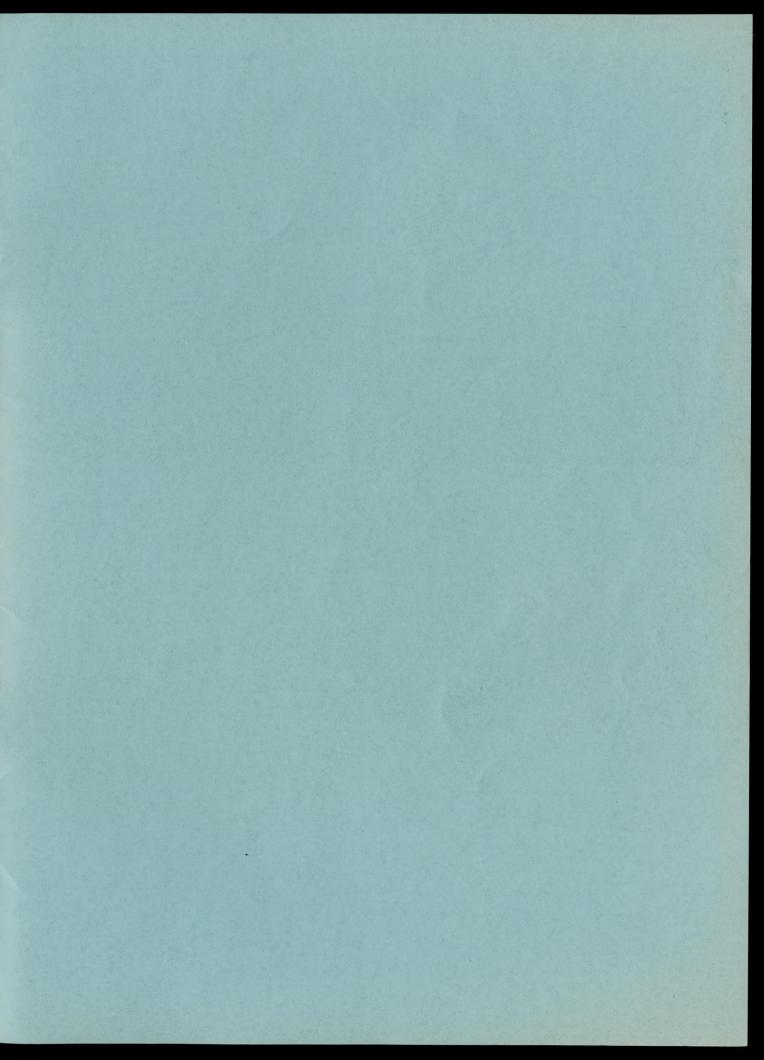
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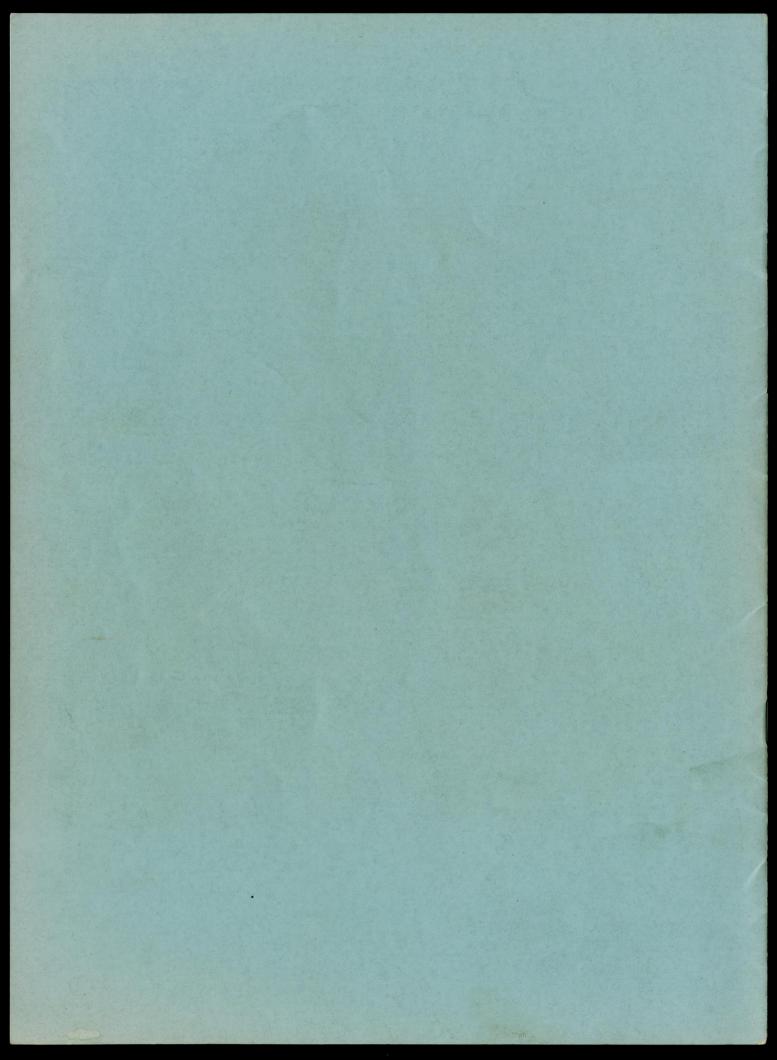
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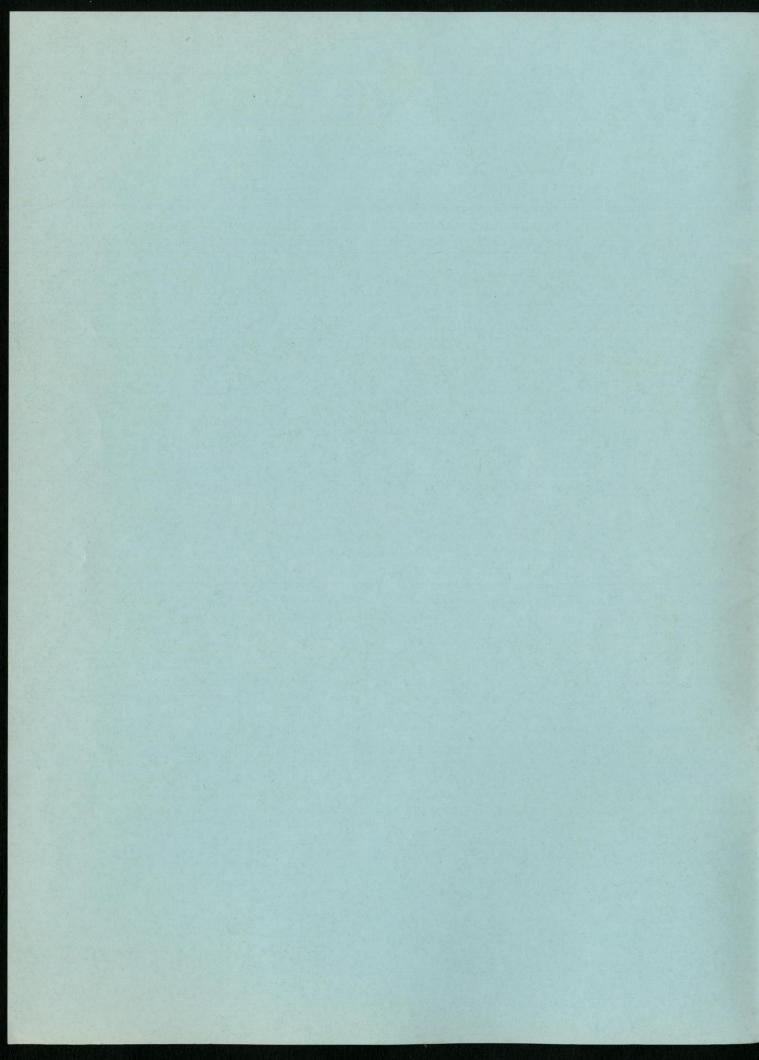




The Discovery of Dicumarol and Its Sequels

By KARL PAUL LINK, PH.D.

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The Discovery of Dicumarol and Its Sequels

By KARL PAUL LINK, PH.D.

THE STORY of Dicumarol* has been told several times by me in the past 17 years, and often by others. Like any good story it need not be told in exactly the same manner each time. In Wisconsin it has become a kind of legend. I shall consider only the high water marks of certain chapters.

Fortunately the basic scientific facts on the discovery and development have already been thoroughly recorded 1-6 so that little new information on Dicumarol and its sequels needs to be revealed here. However, when I do introduce new material it will be restricted to that which is documented or sustainable via memoranda or letters.

The story begins some 36 years ago on the prairies of North Dakota and in Alberta, Canada. In the 1920's a new malady of cattle involving fatal bleeding showed up almost simultaneously in these areas. The veterinarians, Schofield and Roderick, were forced to conclude that the cause of the disease was neither a pathogenic organism nor a nutritional deficiency. The origin of the new malady was traced to stacks of sweet clover hay mysteriously gone bad. Hence the disease became known in veterinary practice as "sweet clover disease" and it was found that it was caused only by improperly cured hay made from the common varieties of sweet clover. When first observed this disease was in a sense without parallel in animal pathology or human medicine. When cattle or sheep ate the spoiled hay the disease slowly became manifest by a progressive diminution in the clotting power of the blood (about 15 days) and resultant internal hemorrhage which usually became fatal in about 30 to 50 days.

It was recognized by Schofield and Roderick that the disease was reversible. It could be controlled in cattle by the withdrawal of the spoiled hay from the diet and by transfusion of blood freshly drawn from normal cattle, provided the hemorrhagic extravasation had not proceeded too far. Indeed, they showed that even in desperate cases, recovery could be hopefully anticipated after transfusion and change in diet (good hay).

In a comprehensive and thorough study of the pathology and physiology of the disease Roderick in 1931 emphasized that the delayed or abolished coagulability of the blood was due to a "prothrombin" deficit. Indeed he showed that the severity of the hemorrhagic condition paralleled the reduction in "prothrombin content or activity." He did this by using the technic developed by that great American pioneer of blood coagulation, the late Professor W. H. Howell. Solutions of what was then called "prothrombin" prepared by precipitation of normal bovine plasma with Howell's acetone method when added to the "sweet clover blood" promoted coagulation. In contrast, preparations of "prothrombin" made in a parallel manner from "sweet clover blood" did not produce coagulation. The other constituents for the maintenance of normal coagulability known at that time (fibrinogen, calcium, platelets, and inhibitory substance) appeared to be unaffected.

I first learned about the hemorrhagic sweet clover disease of cattle in December 1932 through the late Ross A. Gortner, who then

From the Department of Biochemistry, University of Wisconsin, Madison, Wis.

Given February 25, 1958 at the New York Academy of Medicine under the auspices of the Section of Medicine and the New York Heart Association, on the programme, "The Historical and Physiological Aspects of Anticoagulants."

^{*}Dicumarol is the trademark for 3,3'-methylenebis-(4-hydroxycoumarin). The anticoagulant was made available in 1940 and 1941 for clinical use by the cooperative efforts of the Wisconsin Alumni Research Foundation, Madison, Wis., the Abbott Laboratories, North Chicago, Ill., Eli Lilly and Company, Indianapolis, Ind., and E. R. Squibb and Company, New Brunswick, N. J. The official U.S.P. name is bishydroxycoumarin.

headed the Biochemistry Department of the University of Minnesota. He had offered me a post and I had come to St. Paul to consider it. Since the "sweet clover disease" was also a problem in Minnesota it was one of the projects open for study if I chose to accept. It was Gortner who supplied me with the original publications of Roderick. Some attempts had been made in Gortner's department to extract the hemorrhagic agent but they, like those of Roderick and others, had failed.

Curiously, the "official start of our work in January 1933 in cooperation with Professor R. A. Brink and W. K. Smith of our Genetics department was on a different aspect of the sweet clover problem. They sought to develop a strain of sweet clover suitable for Wisconsin climatic conditions low in, or free from, coumarin. Though coumarin smells sweet (the characteristic smell of new mown hay is due to its presence) it tastes bitter, and it was known that the bitter taste of green sweet clover plants, Melilotus alba and M. officianalis, paralleled the total coumarin content. In actual practice it was observable that cattle (or rabbits) would eat the less bitter plants first.

Tragedy out on the Farm

Quite apart from the "official" start concerned primarily with the palatability question my laboratory had a direct catalytic hit from agricultural practice.

Indeed on a Saturday afternoon in February 1933 following the first conferences with Brink, while a blizzard was howling and the mercury was hovering near zero, a farmer from the vicinity of Deer Park, Wisconsin, some 190 miles from Madison appeared with what the late Professor A. J. Carlson might have called "the evidence." Curiously the farmer's name was Ed Carlson. The hemorrhagic sweet clover disease of cattle was rampant on his farm. He had fed sweet clover hay for years previously without encountering any difficulties and he doubted the veterinarian's diagnosis. Accordingly he was advised to go to the Agricultural Experiment Station authorities to get the facts. The office of the State Veterinarian had closed and pure chance had brought him to the Biochemistry Building. Farmer Carlson's multiple evidence was a dead heifer, a milk can containing blood completely destitute of clotting capacity, and about 100 pounds of spoiled sweet clover—the only hay he had to feed his cattle.

His account of the over-all course of the disease coincided perfectly with the classical "sweet clover poisoning" picture. Late in December he had lost 2 young heifers. In January 1 of his favorite old cows had developed a massive hematoma on a thigh and following a skin puncture fatal bleeding set in rapidly. Finally 2 young cows had died on Friday and the bull was oozing blood from the nose. So he took off for Madison in a blizzard.

I immediately had to tell farmer Carlson that we could do no more at this time than to recommend the teachings of Roderick and Schofield. He had to stop feeding that hay, and possibly transfuse those desperately sick cattle, if he wanted to save them. Eventually it might become possible to make some usable recommendations to avoid such disasters, but not now.

I can still see him take off for home about 4:00 p.m. Those 190 miles of drifted roads between our laboratory and his barn must have appeared to him like a treacherous and somber ocean.

I cannot take the time to tell all the details of this slice of the Dicumarol story, but I can assure you its impact on me was immense. I will relate a part of it exactly as I did in my first lecture on Dicumarol given at the Mayo Clinic on March 12, 1942.

When farmer Carlson came to see us, my senior student and old man Friday was Eugen Wilhelm Schoeffel, a volatile Schwabian who came to the U.S. in 1926 with a diploma in Agricultural Chemistry. After serving a 2-year apprenticeship in the Chicago Stock Yards he began to study with me in 1929. Schoeffel is interesting, energetic, and loyal. He was then and still is, somewhat of a mystic and inclined in ordinary conversation to quote freely from Goethe's Faust, Shakespeare, and the Bible, as well as other primary sources. In 1933 his spoken English was not only strongly guttural, but also very earthy, punctuated frequently with Schwabian German.

After farmer Carlson left, Schoeffel stormed back and forth in the laboratory shouting, "Vat da Hell, a farmer shtruggles nearly 200 miles in dis Sau-wetter, driven by a shpectre and den has to go home vit promises dat might come true in five, ten, fifteen years, maybe never. Who knows? 'Get some good hay—transfuse.' Ach!! Gott, how can you do dat ven you haf no money?'' he snarled.

He dipped his hands into the milk can repeatedly and while rubbing them muttered, "Dere's no clot in dat blook! BLUT, BLUT VERFLUCHTES BLUT. 'Die Menschen dauern mich in ihren Jammertagen.' " (Faust Prolog., line 297) and then, "Vat vill he find ven he gets home? Sicker cows. And ven he and his good voman go to church tomorrow and pray and pray and pray, vat vill dey haf on Monday? MORE DEAD COWS!! He has no udder hay to feed—he can't buy any. And if he loses de bull he loses his seed. Mein Gott!! Mein Gott!! Vy didn't ve anti-shi-pate dis? Ya, ve should haf anti-shi-pated dis."

We took the blood and hay and played about with them until about 7:00 p.m. when I headed for home. As I left the laboratory, Schoeffel grabbed me by the shoulders, looked me squarely in the face and said, "Before you go let me tell you something. Der is a deshtiny dat shapes our ends, it shapes our ends I tell you! I vill clean up and gif you a document on Monday morning."

Development of the Bioassay

Two fundamental issues confronted us. First there were no *chemical* criteria available to establish the presence of the hemorrhagic agent. Therefore, a *bioassay* involving a small experimental animal (rabbits)) offered the only practical means of appraising the anticoagulant activity of test hays and extracts prepared therefrom.

It was clear from the pioneer papers of Roderick that the sweet clover disease was completely reversible. The eating of spoiled hay, even over long periods, caused no permanent functional change, no demonstrable morphologic change, and no detectable pathologic change of the liver, the assumed primary site of prothrombin synthesis. Nevertheless,

the immediate prospects of developing a reliable and simple bioassay were not bright; indeed they were dark, "dark like the inside of a cow." We had not had previous experience with that complex problem—blood coagulation.

Schoeffel and Roberts first showed that the Howell method for estimating prothrombin activity did not have the precision required. Smith and Roberts showed that the whole blood coagulation time was too variable, and that the Quick 1-stage method using whole plasma left much to be desired. Smith also showed that there was a wide variation in the response of individual rabbits to the standard dose of 50 Gm. of the spoiled hay. So Campbell and Smith bred and reared a susceptible rabbit colony specifically for the assay.

At that time, 1935-1938, a bloody and amusing polemic raged among the coagulation specialists on how to estimate "prothrombin concentration or activity"-whether it should be done by the 1-stage method of Quick* or the 2-stage method of H. P. Smith and coworkers.1-3, 8 We tried to keep out of that brawl. In 1938 Campbell finally got over the chief obstacles. He adapted the Quick 1-stage method to our conditions, primarily by relying on the clottability of diluted plasma within the concentration range 12.5 to 8.34 per cent. He eliminated some of the inherent daily variations by fasting the assay rabbit 24 to 36 hours before feeding any preparation under test, by making the plasma clottability tests promptly after drawing the blood, and by comparing the test plasma against the normal plasma of each rabbit.

Through the use of individually standardized rabbits (the standard response being that

^{*}The intricacies of the blood coagulation phenomenon are outside the scope of this discourse. Suffice it to state that it is now accepted by most "coagulationists" that a prolonged Quick 1-stage "prothrombin time" (when the fibrinogen is normal) induced by Dicumarol and the like is a primary deficiency in factor VII and prothrombin. See British Medical Bulletin, vol. II, no. 1, Blood Coagulation and Thrombosis, Medical Department, The British Council, London, November (1955), and the lectures by Owren P. A. on Coagulation of Blood, etc., Northwest Medicine, January, pp. 31-39, February, pp. 159-166, and March, pp. 298-307, 1957.

induced by the anticoagulant in 50 Gm. of spoiled hay) and by having the assay on a strictly differential basis the ever present problem of biologic variation was greatly reduced.

Some side observations were made by Campbell on the plasma of rabbits fed the spoiled hay or fractions thereof that were later reported by others. A plasma factor beyond that needed by the classical blood coagulation expression of Morawitz-Field and Spero was hinted at in one of Campbell's reports. But these hares were not hunted. Our goal was to make real a substance that abolished the clottability of cattle blood in agricultural practice. To use the vernacular, the bioassay using the 1-stage plasma clottability was altered so that "it worked," and few of the valuable assay rabbits were lost in the process. One of them known as Bess Campbell was used for about 200 individual assays, over a period of 5 years.

Isolation, Crystallization, Identification, and Synthesis of Dicumarol

Between that fateful Saturday in February 1933 and June 1939 a long and arduous trail was followed by Smith, Roberts, and especially Campbell, to lay the anticoagulant out on the bench. I would like to detail some of the chemical extraction, separation, and isolation problems that the spoiled sweet clover hay presented. This hay was indeed a kind of biochemical grab-bag and yielded many inactive products, some new, most of them old. But suffice it to state that many a seething and simmering hope did not become reality. At times the hemorrhagic agent appeared to hover before us like thistle down only to elude us like the will-o-the-wisp. At one time it was thought to be a porphyrin-like substance, a pheophytin resulting from the degradation of the chlorophyll in the spoiling process.

Finally in the dimness of dawn on June 28, 1939, after working all night, Campbell saw on a microscope slide what turned out to be crystalline Dicumarol. Two hours later he had collected about 6.0 mg. of it.

When I reached the laboratory that morning Campbell was asleep on the laboratory couch; the door to the room was guarded by one Chet Boyles, a soldier of fortune on the W.P.A. relief roles, who assisted Campbell with the bioassays. Boyles was an excellent handler of animals for he had served 2 years as helper to a veterinarian before he came to us.

As I walked into the room, Boyles was taking a nip from the contents of a bottle whose bottom layer consisted of carpet tacks, the upper layer of 95 per cent ethanol. Without the flicker of an eyelash Boyles said to me, "I'm celebrating, Doc. Campy has hit the jack-pot." (As though I didn't know that he had been hitting that bottle for months.)

But Boyles' surmise was correct this time. Campbell did have Dicumarol and the first bioassay to establish its anticoagulant potency was already in process!

Campbell avoided me for 2 days—until the results of the assay were available—and then he came in to report.

There is a bed-rock of matter-of-fact common sense in Campbell's makeup. He was not inclined to show his emotions, but it was apparent that he was secretly as happy as a boy who had just caught his first big fish. He passed the vial to me and said, "This is H. A.!" (H. A. was the laboratory code for hemorrhagic agent.) I did not disclose that Boyles had given me the tip-off. I told Campbell that I knew a couple of lines of German poetry that fitted the occasion, and I recited to him,

"So halt'ich's endlich denn in meine Händen

Und nenn' es in gwissem Sinne mein."

We sent a short wire to Schoeffel, who was then in the control laboratory of the American Medical Association in Chicago. He responded at once with a 200-word reply wherein he expressed his *complete* confidence in Nature, Fate, and us.

Mass isolation was started at once, and a stock of about 1,800 mg. of the crystalline anticoagulant was accumulated (Stahmann).

The problem of determining its structure fell to the sensitive, brilliant, and deft C. F. Huebner, who with some assistance from his lively imagination made the correct structural diagnosis as 3, 3'-methylenebis (4-hydroxycoumarin). He set the sights for the synthesis, which was achieved on April Fool's day, 1940. The synthetic and the natural product were shown to be chemically identical. Subsequently, Overman and Sullivan, through carefully conducted tests on the rabbit, rat, guinea pig, mouse, and dog, hall-marked the natural and synthetic products as biological equals.

The determination of the structure of the anticoagulant as a 3-substituted derivative of 4-hydroxycoumarin makes it appear that both of the undesirable aspects of the common sweet clovers—their unpalatability (bitterness) in the green state and the tendency of the hays to cause hemorrhage when improperly cured—have a common basis in the coumarin molecule. The biological synthesis during spoilage can be rationalized as an oxidation of coumarin to 4-hydroxycoumarin which upon coupling with formaldehyde leads to Dicumarol.

Physiologic Action of Dicumarol

After synthetic Dicumarol became available in quantity the essentials of its physiologic action were quickly established. It was shown that there is a lag in response, a variation in the intensity and duration of the hypoprothrombinemia (plasma prothrombin clotting time), depending on the size of the dose. In each species tested a certain single dose level gives the most efficient response. Below this level the efficiency of action is decreased by a threshold effect and at high levels by incomplete absorption of the drug.

Due to the latent or lag period of 12 to 24 hours before the drug's action becomes apparent, there is a cumulative effect following repeated administration. Thus it was anticipated that in clinical practice this action will

vary with the individual and because of this variation optimal therapeutic effects without hemorrhage would be obtained only when the dosage is individualized.

A brief summary 1-3 of the details follows:

- 1. There is a wide species difference in the response induced in the rabbit, rat, guinea pig, mouse, dog, cat, and chicken, and this varies with the age and sensitivity of each individual. Broadly speaking, the rat and mouse are the most sensitive, the cat and dog intermediate, and the rabbit, the cow, and the chicken the least sensitive.
- 2. The vitamin K and C levels in the diet affect not only the intensity but also the duration of the anticoagulant action. I propose to elaborate on this later.
- 3. The nutritional status of the animal affects the anticoagulant response—fasting generally enhances it in all species.
- 4. Any pre-existing hypoprothrombinemia like that inducible by the salicylates (aspirin), the sulfa drugs, or mild chloroform anesthesia augmented the response.
- 5. The hepatic and renal function influences both the intensity and duration of the response.
- 6. The presence of drugs that affect the total functioning capacity of the liver, like the methylxanthines (theophyllin) and the digitalis drugs, have a mild but definitely detectable counter action.
- 7. Pregnant or lactating females show a slight resistance to the drug's anticoagulant action.

These observations did not exhaust the conditions that can influence Dicumarol's action but they cover the essential points. Finally, it should be added that in Dr. Best's department at Toronto, Dale and Jaques first⁹ and later Meyer and co-workers¹⁰ at Wisconsin General Hospital, and others^{11–13} were able to show that a primary relationship exists between thrombus formation and the clotting mechanism of the blood. These studies established for the first time that an effective reduction of extravascular and intravascular thrombus formation parallels the diminished hypocoagulability induced by Dicumarol, It

was also shown by Spooner and Meyer¹⁴ that, when Dicumarol is given to dogs in safely usable therapeutic doses, it definitely decreases platelet adhesiveness; at the same time Quick showed that it also reduced platelet agglutinability.¹⁵ Thus the clinical use of the anticoagulant as a prophylactic agent for (against) thrombosis rested on a sound experimental basis.

Breaking the Bonds of the Usual Pattern of Thought

When we turned Dicumarol over to the clinicians in the years 1940 to 1942, one significant point, clearly established by our work, was at first missed, in fact denied.6 I have reference to the capital fact that vitamin K (all forms-some better than others) can counteract the action of Dicumarol.* I emphasized this in letters, personal conversations, and in my first lecture on Dicumarol at the Mayo Clinic and at Wisconsin General Hospital. In spite of these efforts the first clinical reports carried the statement that "vitamin K has no effect as an antidote to the administration of Dicumarol." The editorial and annotation writers for the medical journals, those who only "think" but "don't try," innocently reiterated this statement. 1, 2 While in error, the clinicians were in good company, for an authority on blood coagulation16 had written in 1937, and again in his book published in 1942, that "vitamin K will not restore the prothrombin concentration" depleted by Dicumarol.17

Originally these denials made me very unhappy. The misfortune of being accused of error was not the primary basis for the unhap-

Normal bull Spoiled sweet clover hay Vitamin
$$K_1$$
 concentrate a completely reversible reaction.

piness, for we were certain that the antidotal capacity of vitamin K would in time be sustained in the clinic. What did disturb me was the needless induction of the hemorrhagic "sweet clover disease" in man and the stigma temporarily attached to Dicumarol, that it was a dangerous drug.¹⁸ And this did happen.

A feature of science that has always appealed to me is that sooner or later, and usually sooner, "the truth will conquer."

Dr. Shepard Shapiro in New York City was the first clinician (February 1942) to sustain our claims that vitamin K can counteract the anticoagulant action of Dicumarol in man when liver function is adequate.^{5, 20} Subsequently he was independently supported by Townsend and Mills in Canada,²¹ Lehman in Sweden,²² and finally by Cromer and Barker²³ at the Mayo Clinic, as well as others. Today it is accepted that the water-soluble forms of vitamin K or vitamin K₁ given orally can successfully antidote overdosing with Dicumarol, provided they be employed when reversal is still possible.

Let us briefly examine why the error arose. The clinicians did not use a 1-stage prothrombin assay as sensitive as the one Campbell developed for our experimental animals. They were originally conditioned to the low levels of vitamin K effective in obstructive jaundice, biliary fistula, cholemic bleeding, etc. It was also thought that the menadione form of vitamin K might be toxic. Over 10 years were required to wipe out this error from clinical practice.

To summarize, surmise, faulty thinking, and not enough trying kept vitamin K from being the corner building stone in Dicumarol therapy that it deserved to be from the outset.

In 1950 Marple and Wright (pages 149 and 181)⁶ wrote, "When bleeding occurred from the clinical use of Dicumarol the fault rested with the physician who administered the drug."

Enthusiasm-Muddle-Consolidation

Within 2 years after Dicumarol was synthesized, over 100 related 3-substituted 4-hydroxycoumarins were prepared in my lab-

^{*}For an account of how, in January 1939, a bull desperately sick from eating spoiled sweet clover hay (he was ''down,'' blood was oozing from the nose, and a massive hematoma adorned the right thigh) was rescued from the clutches of death via a vitamin K_1 concentrate prepared from alfalfa hay, see reference 2. Originally not even this ''bull story'' could break the bonds of the usual pattern of thought. The equation is

oratory. Synthesis ran substantially ahead of biochemical appraisal. Accordingly, when I gave the Harvey Society lecture on "The Anticoagulant from Spoiled Sweet Clover Hay" in January 19441 it was indicated that "it would not be valid to conclude from the relative appraisals on activity made with the rabbit-that Dicumarol is the most desirable compound for clinical use." It was indicated that "In the course of the routine appraisal of the many compounds tested it was learned that some of them exhibited a slower but more sustained hypoprothrombinemic action, while the action of others is of shorter duration. It will take some time before final judgment can be passed on this subject. From the experience gained with other pharmacological agents it is abundantly clear that the final test is the action in man under a variety of conditions. The unpredictable can be surprising, so, as we see it, we might now be at the beginning of things and not at the end in this field of study."

Being an agriculturist I have little confidence in predictions, including my own. The situation can now be appraised in the light of wisdom after the event. Bear in mind that the statement quoted was made less than 4 years after Dicumarol became known to us and before extensive clinical information on the response in man was available. About 50 reports on the clinical use of Dicumarol had appeared between 1941 to 1944.^{5, 6*}

The appearance of any new drug creates an interesting cycle of events, and Dicumarol went through that cycle quite rapidly. The first preliminary reports indicated that an atmosphere of optimism prevailed. They evoked

prompt favorable editorial comment in the Lancet (September 13, 1941) under the title, "Heparin and a Rival." Then came the second period—a period of muddle. Enthusiasts and skeptics for anticoagulant therapy with Dicumarol were created, and it can be stated that some of the skeptics condemned the drug in no uncertain terms, though they were largely armed with surmise, faulty, or no prothrombin clotting time determinations and they used the antidote vitamin K inadequately. Then came the third period of consolidation, from which it can now be concluded that a better anticoagulant of the Dicumarol type was desired.

Since Dr. Wright asked for aspects of human interest, let me add another slice from the Dicumarol story. Early in September 1945 I was fed up with laboratory work, etc., and I went off on a canoe trip with my family. On this trip we were caught in a cold rain storm. I got soaked and overexhausted. Two weeks later I came down with what I had had once before-after a similar heavy physical bout, as a student in Switzerland-wet pleurisy. At first my doctor thought I had pneumonia; then I told him about my previous bouts of tuberculosis; so the diagnosis was changed to reactivated pulmonary tuberculosis. I spent 2 months at Wisconsin General Hospital and then was transferred to Lakeview Sanatorium headed by the double cross of Lorraine. Here I was supposed to vegetate like a topped carrot. I did rest there, physically for 6 months, took nothing stronger than cod liver oil and 3 bottles of beer a day, but kept the aged tuberculosis out of my mind by studying laboratory records and reading the history of rodent control from ancient to modern times.24, 25

A "Janus" in the Coumarin Family

Now brace yourselves, for I propose to shift from a "cow poison" that had become a drug of substantial clinical usefulness, to a "rat poison" converted to a drug, which has I believe most of the desirable features that can be expected from an anticoagulant to be given primarily via the oral route.

^{*}The first clinical report to appear was by Butt, H. R., Allen, E. V., and Bollman, J. L.: Preparation from spoiled sweet clover (3,3'-methylene-bis-4-hydroxycoumarin) which prolongs the coagulation and prothrombin time of blood: Preliminary report of experimental and clinical studies, Proc. Staff Meet. Mayo Clinic 16: 388-395 (June 18), 1941. See also Allen, E. V., Barker, N. W., and Waugh, J. M., J.A.M.A. 120: 1009, 1942; Wright, I. S., and Prandoni, A., J.A.M.A. 120: 1015, 1942; Bingham, J. B., Meyer, O. O., and Pohle, F. J., Am. J. M. Sc. 202: 563, 1941.

The many coumarins synthesized between 1940 and 1944 were listed by numbers in logical groups based on their chemical structure.1 While I was in the sanatorium in 1945-1946 the laboratory work was practically at a standstill. There were few students available, since most of them were still in the armed forces. So I had ample time to reexamine all the chemical and bioassay data available. Upon the return of L. D. Scheel from service in the spring of 1946, he was assigned to the task of reappraising the anticoagulant activity of the compounds numbered from 40 to 65. They were made by Ikawa in 1942-43. Instead of using only rabbits for the bioassays Scheel also used rats, mice, and dogs. In 1946-1948 he defined coumarin numbers 42 and 63 as being much more potent than Dicumarol in the rat and dog, as capable of producing a more uniform anticoagulant response, and as having the quality of maintaining a more severe state of hypothrombinemia without inducing visible bleeding. Certain chemical properties were also considered: the degree of purity readily attainable (absence of taste and odor), the cost of making them, and the property of being convertible to stable water-soluble salts.

Back in 1940 to 1942, Overman, Field, and my colleague, C. A. Bauman, had studied extensively the action of Dicumarol in the laboratory rat, and the effect of diet on the response, specifically the influence of vitamin K and foods rich in it. Later in 1942 I personally, with the help of good old Schoeffel, set up field trials to ascertain the suitability of Dicumarol for rodenticidal purpose. It was concluded that the activity of Dicumarol in the rat was not high enough to make it practical for rodent control. This was found to be largely due to the vitamin K content of mature grains and the availability of green foods with a high vitamin K content. It was shown that rats could tolerate a daily intake of 2.0 mg. of Dicumarol for 60 or more days due to the vitamin K content of the natural foods available. On a semisynthetic diet essentially free from vitamin K the survival time was about 15 to 23 days. When 5 mg. of vitamin K per day were added to the artificial diet, the rats also tolerated 2.0 mg. of Dicumarol daily for over 60 days.

Early in 1948 I told Scheel and Dorothy Wu that I wanted to propose no. 42 for rodenticidal use. 24, 25 This proposal shook the laboratory. I can sum up by stating the consensus of opinion "the boss has really gone off the deep end this time." Scheel favored no. 63 for clinical purposes. They are chemically closely related, no. 63 being a direct derivative of no. 42. To make a long story very short, early in 1948 no. 42 was promoted for rodent control under the auspices of the Wisconsin Alumni Research Foundation through the able, enthusiastic, and publicspirited Ward Ross, General Manager of this organization. Within a short time this effort revolutionized the art of rodent control (multiple doses as opposed to the single dose of the highly toxic poisons), and warfarin rapidly became and still is the leader in the rodenticide field.* The name Warfarin was coined by me by combining the first letters of the Wisconsin Alumni Research Foundation with the "arin" from coumarin-and it is now a household word throughout the world.**

Between 1948 and 1952 Dicumarol was, so to speak, being squeezed by chemical kin stemming primarily from European studies.²⁶ "Imitation is the sincerest form of flattery." Curiously, one of them, a derivative of Dicumarol, trade-named Tromexan, was not seriously considered by us as early as 1940. Though it acted somewhat faster than Dicumarol, it required substantially larger doses

^{*}Just as cattle eat hemorrhagic sweet clover hay until they die without visible sensory responses, the rat eats warfarinized cereal grain bait until fatal hemorrhage sets in. Neither bait refusal nor bait shyness develops. Indeed, the rodent's departure is biblical "death without sting." In Maxwell Anderson's drama, Elizabeth the Queen says, "To the end of time it will be so . . . the rats inherit the earth." Since warfarin has become available, this need not be so. Furthermore, via the water-soluble warfarin sodium the rat can drink unto death.

^{**}Warfarin is the safest rodenticide known. Up to now, in the United States there is no recorded case of a warfarin-induced fatality in man, although over 140,000,000 pounds of warfarin containing bait (0.025 per cent) have been distributed since 1950.

to get the equivalent anticoagulant action.* The second, Marcumar, a close kin to warfarin, was also passed by us, since its water-soluble sodium salt is less stable than warfarin sodium. Milligram for milligram, Marcumar is more active than warfarin and its action is also more prolonged. But as a result of the claims made about Tromexan and Marcumar

*The clinical promotion of Tromexan (bis-3,3'-4-oxycoumarinyl) ethyl acetate, referred to as B.O.E.A. in the article by Burt, C. C., Wright, H. P., and Kubik, M., Brit. M. J. 2: 1250, 1949, precipitated interesting editorial comment under the heading, Dangers of Dicumarol (pp. 1279-1280). In this editorial it was suggested that since Tromexan seemed to be superior to Dicumarol "owing to its shorterlived action . . ." and in view of recent reports of the drug's (Dicumarol's) efficiency as a rat poison, it may be that Dicumarol will ultimately be more useful for that purpose."

Unfortunately the significance of our paper on the action of Dicumarol in the rat dealing specifically with the effect of diet and vitamin K on the anticoagulant action (J. Nutrition 23: 589-602, 1942) was not appreciated by O'Conner, J. A., Research 1: 334, 1948, who suggested the use of Dicumarol for rodent control. Had O'Conner read our paper carefully, he would not have made this suggestion. The critical issue is that Dicumarol's anticoagulant action in the rat subsisting on natural grain foods is too slow to be practical. The level of Dicumarol in the bait has to be set so high that other animals (cat, dog) and children (accidental ingestion) would be vulnerable.

It was the inefficiency and slowness of Dicumarol to kill rats under practical field conditions that caused me not to suggest its use as a rodenticide in 1941-1943 (letter, Link, K. P., to the National Defense Research Council, Washington, D.C., dated March 10, 1943, and confidential disclosures, 1942-1943, to the late Professor Homer Adkins and Professor H. Gilman, official investigators and project leaders of N.D.R.C. and O.S.R.D. (confirmatory letter of Gilman to Link, June 11, 1952). Instead of Dicumarol the much more potent and efficient (no. 42) warfarin was recommended. Nevertheless, O'Conner's paper served a useful purpose in rodenticide control circles, and he must be accredited with being the first one to stimulate, via the printed page, the backward pest control workers by pointing out the potentials of anticoagulants (Link, K. P., letter December 6, 1948, to U.S.D.I. Fish and Wildlife Service, Denver, Colo.). I had attempted to create an interest in warfarin via letters and memoranda, which at first failed to reach the objective (see reference 24 and particularly reference 25). A complete history of the warfarin development based on 10 years of practical field experience is in the process of being prepared.

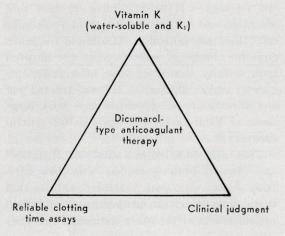
I took another good look at the mass data in the light of what clinicians were seeking, namely an anticoagulant that could be used via any route with the retention of the virtues of Dicumarol but without its limitations.

Based in part on the supposition that the response of the rat to warfarin (no. 42) was a very reliable index of how man would respond, late in 1950 I told Dr. S. Shapiro and Dr. O. O. Meyer that the water-soluble sodium salt of warfarin should be tried on man. In 1941 the clinicians had literally snatched the "cow poison" from us, but the transition to a substance originally promoted to exterminate rats and mice was a bit more than they could accept with real enthusiasm. Then, on April 5, 1951, we were informed by Captain J. Love (MC) in the U.S.N. at Philadelphia that an army inductee was admitted to the Naval Hospital who had taken over a period of 5 days a concentrate of warfarin designed for rodent control.²⁷ The package contained 567 mg. of warfarin in corn starch. The inductee had followed the multiple dose directions on the package. It became clear to him that warfarin was not an efficient agent "to shuffle off" this "mortal coil." It allowed too much time for thinking-so he went to the hospital with a fully developed case of hemorrhagic "sweet clover disease." He was treated per the directions-blood transfusion and large doses of Vitamin K-and made an uneventful recovery.28

This incident acted as a catalyst. Shapiro²⁹ and Meyer³¹ both concluded from their carefully done work with warfarin sodium that it did possess certain properties not inherent in Dicumarol or the other anticoagulants they

had tried. After Collin Schroeder perfected the process of making warfarin sodium, I induced my long-standing friend, Dr. S. M. Gordon, of the Endo Laboratories, Richmond Hill, N.Y., to make it available for clinical use. This he did, under the trade name Coumadin Sodium. Today it would appear, from the 15 to 20 clinical papers on warfarin sodium that have been published (see reference 32), that most of the drawbacks of Dicumarol have been overcome. Warfarin sodium is at least 5 and possibly 10 times more potent than Dicumarol. It is the only synthetic anticoagulant available today for therapeutic anticoagulation that can be given orally, intravenously, intramuscularly, or rectally.³² The rate of absorption is almost the same, irrespective of how it is administered. No other anticoagulant of the Dicumarol type has all these virtues. Of course, an overdosage can be readily corrected via vitamin K. It acts faster than Dicumarol, and fewer prothrombin times are required in its routine use. To use the words of both Shapiro and Meyer, "It is easier to handle clinically." It is my firm belief that in time it will replace Dicumarol on the basis of its performance over a wide variety of conditions and that other anticoagulants of the Dicumarol type will not be superior.

It always seems appropriate to me to visualize successful anticoagulant therapy with the Dicumarol-type drugs as being shaped like a triangle with accurate "prothrombin assays" at one corner, vitamin K at another, and sound clinical judgment at the third.



Each corner is linked to the other by way of the connecting sides. There should be no separation, each is vitally dependent on the other two. Though the clinical judgment be good and the "prothrombin time" accurate, the vitamin K corner might still have to be evoked, since each individual patient is essentially "an unstandardized biologic entity," errors in dosage can be made by the hospital service, the patient might have a silent ulcer, or the functioning of the liver or kidney might unknowingly be penumbral.

On September 29, 1955, I got a card from a former Wisconsinite working in Fitzsimons Army Hospital in Denver, Colorado which read, "The President is getting one of your drugs and it's not Dicumarol." A day later press secretary J. C. Hagerty announced,33 "The heparin which was used initially as the anticoagulant has been replaced by a drug of the Dicumarol type. The present prothrombin level has been well maintained." I knew of Colonel Pollock's paper, "Clinical experience with warfarin (coumadin sodium a new anticoagulant)," read before the first annual meeting of the American College of Angiology Atlantic City, N.J., on June 4, 1955, and I surmised that the most important man in the world today was being anticoagulated via warfarin sodium.34 This surmise proved to be correct and since then it is an open secret that warfarin sodium was being used. "The unpredictable can be surprising."

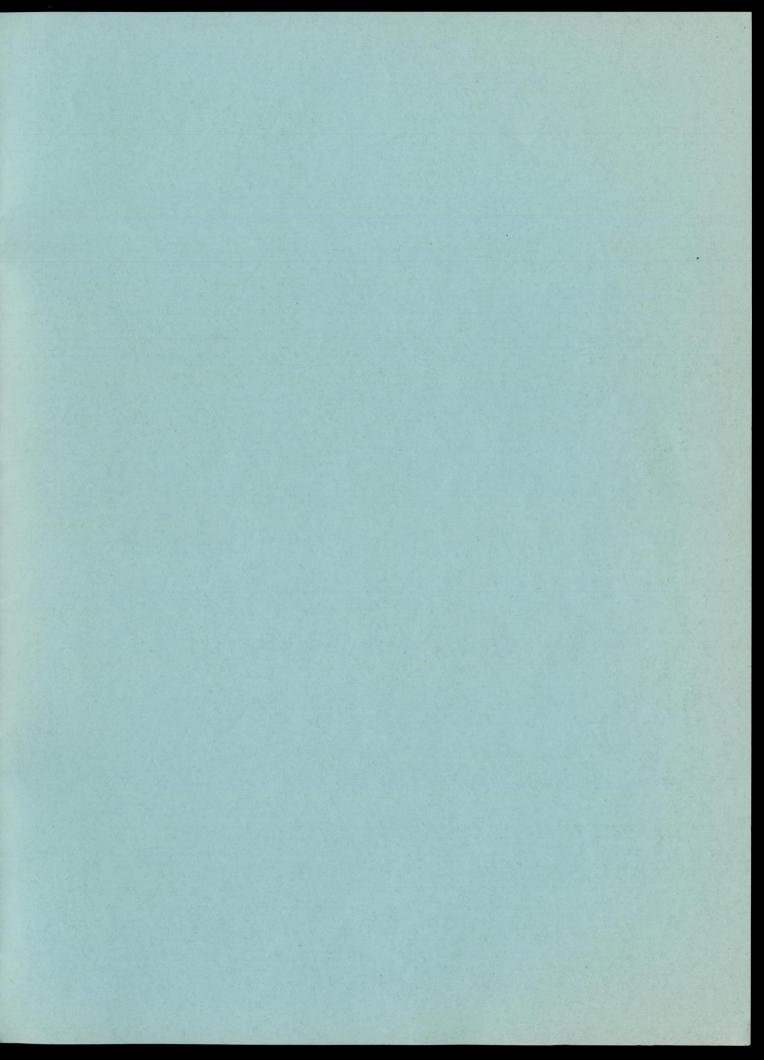
In closing I wish to indicate that what my laboratory has achieved in the past $2\frac{1}{2}$ decades represents the combined effort of many students. It is fun to be the reporter or narrator of this highly successful adventure. To use the words of the late Allan Gregg, my students represented much "emergent ability." I think the secret of their success is 3-pronged: they never ceased to wonder, they kept on trying, and they were on a project directed toward doing mankind some good instead of trying to destroy it.

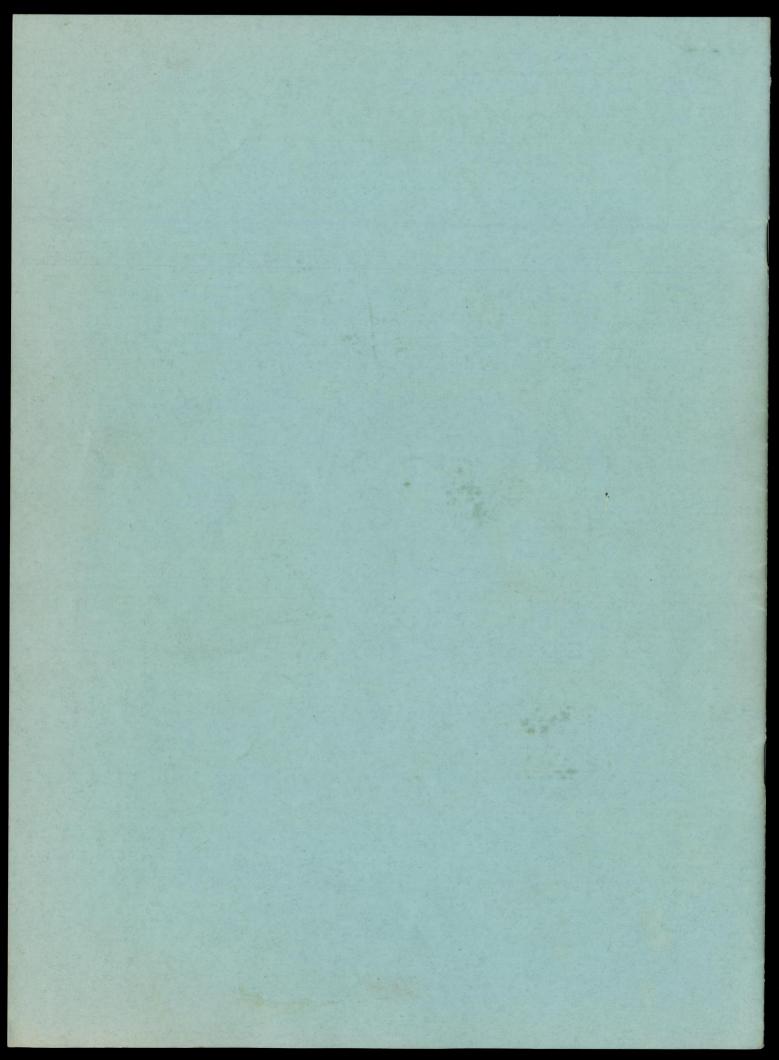
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U. W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN RELEASE:

6/3/58 cfg

Immediately

MADISON-Doctors from as far away as Hawaii as well as from the four corners of the United States have sent in registrations for the annual University of Wisconsin Medical Alumni Day Thursday, June 5. Advance registrations total well over 100.

Morning activity will feature members of the UW faculty and the annual business session of the Medical Alumni group. Appearing on the morning program will be Drs. O. O. Meyer, Karl Link, Joseph Gale, Carl Fellner, and Edward Albright.

Dr. Conrad A. Elvehjem, University president-elect, will welcome the group at the afternoon session. Dr. Gunnar Gundersen, of LaCrosse, American Medical Association president-elect, will deliver an afternoon address, "Medicine, 1958, USA."

Dean John L. Parks, UW alumnus and present head of the George Washington University School of Medicine, will speak to the group on "Microbes, Midwivery, and Modern Obstetrics."

Presentations by representatives of the three reuning classes--1928, 1938, and 1948--will occupy the remainder of the afternoon. Class representatives are Dr. Alexander D. Spooner, urologist from Milwaukee, ('28), Dr. John H. Wishart, internist from Eau Claire, ('38), and Dr. Horace Gerarde, faculty member at Rutgers University, ('48).

The day's activity will wind up with dinner and a social mixer at the Club Chanticleer in Middleton at 6:30 p.m. Dr. Einar Daniels, medical alumni president from Milwaukee, will preside.

WARFARIN ADVERTISING CAMPAIGN - WARF - 1957-1958

CONSUMER JOURNALS

1957

1958

AG. LEADERS' DIGEST	November and December	Jan., Feb., March
AMERICAN FARM YOUTH MAG.	November	Jan., Feb., March
CAPPER'S FARMER	November	January
COUNTY AGT. & VO-AG TCHR.	November and December	February and March
DAKOTA FARMER	October 5	January 18
FARM & RANCH-SO. AGRI.	November and December	January
FARM JOURNAL	November and December	January
FARMER, THE	Oct. 5, Nov. 2, Dec. 7	January 18
HOARD'S DAIRYMAN	Oct. 25, Nov. 10	
KANSAS FARMER	Oct. 5, Nov. 2	
NATIONAL 4-H NEWS	November	January and March
NATIONAL FUTURE FARMER	DecJan. issue	FebMar., AprMay
NEBRASKA FARMER	Oct. 5, Nov. 2, Dec. 7	January 18
POULTRY TRIBUNE	November	
PRAIRIE FARMER	Oct. 5, Nov. 2, Dec. 7	January 18
PROGRESSIVE FARMER	November and December	January
SUCCESSFUL FARMING	November and December	
WALLACE'S FARMER &		
IOWA HOMESTEAD	Oct. 5, Nov. 2, Dec. 7	January
WEEKLY STAR FARMER	Oct. 2, Nov. 6, Dec. 4	
WIS. AGRI, & FARMER	Oct. 5, Nov. 2, Dec. 7	January 18
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TRADE JOURNALS		
DRUG TOPICS	Oct. 14, Nov. 25	January 6
FEED BAG, THE	Oct., Nov., Dec.	Jan., Feb., March
	(Oct. 12-19-26	
FEEDSTUFFS	(Nov. 9-16-23-30	Jan. 11-18
	(Dec. 7	
HARDWARE AGE	Oct. 24., Nov. 7-21	January 16
PROGRESSIVE GROCER	November and December	

U. W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN RELEASE:

Immediately

MADISON, Wis.--A University of Wisconsin-developed synthetic drug, Warfarin (Coumadin) sodium, comes closer to being an ideal anticoagulant than any other drug now available, according to three groups of researchers reporting in two medical journals this fall.

Warfarin sodium, one of the most widely-used anticoagulants today, prevents death-dealing blood clots in heart attacks and certain kinds of circulatory diseases by depressing the blood's ability to clot.

The medical groups found that Warfarin sodium has a faster and more lasting effect and produces fewer harmful side effects than other anti-coagulants. Work of two groups was reported in separate articles in the Nov. 16 Journal of the American Medical Association. The third article appeared in the October issue of Angiology.

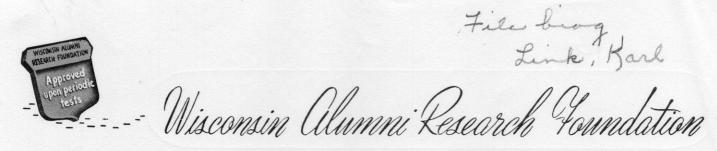
Warfarin sodium was discovered and synthesized in the laboratories of the UW's internationally famous biochemist, Prof. Karl Paul Link. Its development stemmed in part from the aim of providing a drug with more predictable responses than the parent compound, the anticoagulant Dicumarol, also discovered by Link.

Clinical evaluation was begun in 1952 by Endo Laboratories and the drug is now made by the firm under license by the Wisconsin Alumni Research Foundation (WARF).

Warfarin sodium is unique because it is effective when given orally, intravenously, intramuscularly, or rectally, according to Drs. Shepard Shapiro and Flavio E. Ciferri, New York City. Other anticoagulants are effective only when given orally.

This property is especially important for persons unable to swallow pills because of heavy sedation, shock, nausea, vomiting, or other reasons.

The researchers also pointed out that Warfarin sodium rarely causes excessive depression of the ability of the blood to clot, with resultant hemorrhage -- one of the problems encountered in some of the other anticoagulants. Excessive depression was quickly counteracted by administration of vitamin K.



P. O. BOX 2217 506 N. WALNUT STREET MADISON 5, WISCONSIN TELEPHONE: ALPINE 7-1026

October 17, 1957

To Warfarin Formulators:

Since 1952 the Foundation and its warfarin licensees—Prentiss Drug & Chemical Co. and S. B. Penick & Co.—have supported warfarin advertising campaigns in farm papers. The major purpose of these campaigns has been to continue reminding the consumer that warfarin is the rodenticide of choice and the product he should buy.

This Fall the Foundation and its warfarin licensees have undertaken a campaign larger in scope than any of those previously carried on The enclosed folder shows the three consumer ads which have already appeared in some farm papers, and which will appear frequently during the balance of 1957 and until the summer of 1958 in the publications listed on the folder. Note that we have continued to use the cartoon type approach as an attention-getter, but that this year, since the ads are larger, we have been able for the first time to use more selling text than heretofore.

We believe that you will agree that this series of ads will provide powerful support for your promotional efforts on your warfarin product at the consumer level. In addition, we are continuing the practice adopted last year of including an ad, likewise depicted in the enclosed folder, in important dealer publications.

From past experience we have learned that many aggressive formulators have found good use among their distributors and dealers for the folders, such as the enclosed, sent out each fall describing these warfarinconsumer campaigns. Therefore, for your convenience, this year the enclosed folder is prepared in the form of a selfmailing piece. If you feel that you can use supplies of this folder among your distributors or dealers, let us know promptly and we shall supply copies.

It is perhaps unnecessary to call to your attention that no manufacturer or marketer of competitive anticoagulant rodenticides lends support to its customers in any way comparable to the support being rendered you as a warfarin formulator by the Foundation and its licensees. We hope that these efforts will be an important factor in enabling you to constantly expand your warfarin sales.

Very truly yours

Ward Ross

Managing Director

WR rt Enc.

MADISON NEWS

7/19/56 jl

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

RELEASE:

Immediately

Prof. David E. Green of the University of Wisconsin's Enzyme
Institute has been invited to deliver one of the 1957 Harvey Lectures in
New York City.

The Harvey Lectures are an annual series of invitational lectures by outstanding scientists delivered before The Harvey Society of New York under the patronage of the New York Academy of Medicine.

The topic of Prof. Green's lecture will be the work of the Enzyme Institute since 1948 on organized enzyme systems. He will deliver the address in April of 1957.

Two other University of Wisconsin scientists have delivered Harvey lectures in the past, Conrad A. Elvehjem and Karl Paul Link.

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FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

10/31/55

RELEASE:

Tuesday, Nov. 1

NEW YORK, N. Y .- Karl Paul Link, professor of biochemistry at the University of Wisconsin, will be granted one of the 1955 Lasker Awards by the American Public Health Association for his "outstanding achievement in medical research."

Selection of Link and 13 other scientists as Lasker Award recipients was announced yesterday by Dr. Herman E. Hilleboe, president of the health association.

Only one other scientist, Dr. Robert D. Defries of the University of Toronto, was granted a Lasker Award for individual effort. Four of the six selections were for scientific team or group accomplishments.

The Lasker Awards are considered to be among the nation's highest medical honors, and have been presented for the past 10 years.

Link was among those selected to receive the award this year for his "fundamental contributions to our understanding of the mechanism of blood clotting and for the development of methods for the improved treatment of thrombo-embolic conditions."

Link is known for his work in isolating the anticoagulant dicumarin, now used throughout the world to prevent the formation of unwanted blood clots following surgical operations and for the treatment of other conditions.

Lasker Award winners will receive monetary prizes of \$1.000, in addition to gold statuettes of the Winged Victory of Samothrace and leather-bound citations. The awards will be presented Nov. 17 at the 83rd annual meeting of the American Public Health Association in Kansas City.

ad one--Link

The 1955 Albert Lasker Awards were also conferred on:

Dr. Defries, director, Connaught Research Laboratories, University of Toronto, Canada, for his leadership in preventive medicine and public health in Canada. Connaught, under Dr. Defries, developed and supplied nearly all the virus used in the Salk poliomyelitis vaccine field trial in 1954;

Dr. C. Walton Lillehei, associate professor of surgery, University of Minnesota, a joint award with Drs. Morley Cohen, Herbert Warden and Richard Varco, the same institution, for "advances in cardiac surgery making possible more direct and safer approaches to the heart";

The Menninger Foundation and Clinic, Topeka, Kan., a group award citing Drs. Karl A. and William C. Menninger for "a sustained and highly productive attack against mental disease, bearing fruit in better hospitals, better trained staffs and greatly improved care of the patient";

The Nursing Services of the U. S. Public Health Service, Washington, D.C., a group award citing the Misses Lucile Leone, Pearl McIver and Margaret Arnstein, for "distinguished contributions to the advancement and well-being of the nation through their leadership in public health nursing";

A tuberculosis research team, composed of Drs. Walsh McDermott and Carl Muschenheim, New York Hospital-Cornell University Medical Center, New York, Drs. Edward H. Robitzek and Irving J. Selikoff, Seaview Hospital, New York, together with Hoffmann-La Roche Laboratories, Nutley, N. J., and the Squibb Institute Laboratories, New York, for "contributions of the first order to our knowledge of the principles of the treatment and control of tuberculosis" with the isoniazid drugs.

Describing the prize-winning achievements, the Lasker Awards Committee noted that Dr. Link triggered a series of revolutionary developments in arteriosclerosis, the nation's number one heart disease killer, with his discovery of dicumarin. This drug, together with its successors, is used to combat intravascular clotting, thrombosis and pulmonary embolism.

ad two--Link

Professor Link is also honored for his discovery of the potent rodent poison. Warfarin, which has played a major role in public health work internationally, the committee pointed out.

Albert Lasker Awards of the American Public Health Association have previously gone to 51 scientists and public health leaders and 16 medical groups. Eight individual Lasker Award winners have later received Nobel Prizes.

The citation to Link's award follows:

"It had long been recognized that the ingestion of spoiled sweet clover produced hemorrhagic disease in cattle, but the responsible agent was unknown. Professor Link accepted this challenge about 1933 and after seven years of intensive investigation reported the successful culmination of his work and that of his co-workers with the recognition, isolation and development of the formula and synthesis of dicumarol in a classic series of papers.

"This opened a gateway to the further study of the mechanism of blood clotting and to the treatment of many important diseases of the heart and blood vessels for which little had been done in the past.

"Clinical investigators in all civilized countries have continued to use this drug for increasing numbers of patients. His work also encouraged others to develop new compounds with similar actions. Dr. Link and his co-workers have continued their investigations and have reported the actions of additional compounds which are being used clinically today.

"In view of the vast number of individuals affected by thromboembolic diseases each year and the fundamental steps taken by Dr. Link toward the solution of these problems, he has earned the deep gratitude of the medical profession and the lay public of this and coming generations."

Fill Raul Links October 10, 1955 Mr. Harold Mantell 126 East 56th Street New York 22. New York Dear Mr. Mantell: Sorry for the delay in answering your letter concerning Karl Paul Link's staying over in New York an extra day for the Life interview, but Prof. Link has been awaiting the call from the regional Life representative, who has apparently not yet appeared. I am enclosing the copy of Prof. Link's reply to my request (and I forwarded your letter to him to more fully explain the situation), and lathough it appears somewhat pessimistic I have the feeling that if some personal contact was made, he would be quite willing to stay over. This hunch is the result of having known him for some time. I am positive he would make an extremely colorful subject for a Life article. Just about the most colorful I could think of. Thanks for your interest in the matter, and we are looking forward to receiving an advance copy of your release so we can mail one for the local papers at the time of the Lasker Award. Best regards. Sincerely. James A. Larsen Science Editor JAL:mjo Encl.

Harold Mantell

Dear Mr. Mantell;

Sorry for the delay in answering your letter concerning Karl Paul Link's staying over in New York an extra day for the Life interview, but Prof. Link has been awaiting the call from the regional Life representative, who has xxxxxx apparently not yet appeared.

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Thanks for your interest in the matter, and we are looking forward forward to receiving an advance copy of your release so we can prepare one for the local papers at the time of the Lasker Award.

Mail

est regardaxuegava regards.

Sincerely

JL

Enclosure x(kix (Copy of Link's letter to me)

NOTE FROM T

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

Can you stay over thru Turl? Obase return letter to me with the censeuer.

Best. Dein ALBERT AND MARY LASKER FOUNDATION, INC.
CHRYSLER BUILDING, NEW YORK 17, N.Y.
TELEPHONE LEXINGTON 2-9391

Please reply to:

Harold Mantell 126 East 56th Street New York 22, N. Y. Tel. EL 5-4533

September 16, 1955

AIR MAIL

Mr. Robert Taylor Director, News Office University of Wisconsin Madison, Wisconsin

Dear Mr. Taylor:

This is to advise you confidentially that the editors of Life Magazine are very much interested in the forthcoming Albert Lasker Award to Dr. Karl Paul Link. Please advise Dr. Link that a regional Life representative may be calling on him shortly and not to be alarmed thereby.

Also, would you ask Dr. Link whether he can arrange to stay over in New York an extra day, that is, through Tuesday, November 1. The Life science staff would like very much to lunch with him that day. We are assuming, of course, that he will be in town for our own Lasker Awards press luncheon on October 31.

Looking forward to hearing from you and with many thanks,

Sincerely,

HAROLD MANTELL Consultant,

Albert Lasker Awards

HM: al

P. S. As we both know from past experience, the fact that Life may be interested does not necessarily mean that Life will print. However, these are the fortunes of publicity and I think in this instance full cooperation is justified by the apparent ardor of the Life people, who share with me the conviction that Dr. Link has been far too little celebrated for the magnitude of his accomplishments.

Dear Jun:

The enclosed letter from H. Mantell has by design been left manswered tell naw awaiting some life from Life. To date no andor has been shown by the regional representative from Life. These "Life Men" are always very Vague - and so

I am left dangling in meertanty.

Jam going to be in New York City on Monday October 31 to attend the officially arranged fress canference that the American Public Health Association is to hold. This I regard as an obligation to the a.P. H.a.

It would appear to me that the material your sent to the a.P.H.a. covers the work - and so I am flaming on learning New York City Monday October 31 about 400 or 4.30 P.M. Cardrally yours

There a family:

James a Lanen. U. news Service. Ols Hill. Fil: Karl Paul benk

Information - Re: Lasker Award 1955

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FEATURE STORY

3/4/55

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

Immediately

RELEASE:

John Kailin Link, 12th grade student at Wisconsin High School, has just received a certificate of achievement for outstanding work in mathematics.

John solved four out of five problems in a national mathematical competition to merit his award from the Mathematics Student Journal, published quarterly by the National Council of Teachers of Mathematics with the cooperation of the Mathematical Association of America.

The journal is a four-page periodical containing problems in mathematics for the enterprising high school student to solve.

The son of the University of Wisconsin Prof. Karl Paul Link of the biochemistry department has a "keen analytical mind and ability and interest to follow through," according to his teacher, Gordon Mock, UW counsellor of education and math teacher at Wisconsin High School. The problems solved involved the use of trigonometry, advanced algebra, and the law of the cosine.

Here is a sample of one of the problems John solved:

"A stack of cannon balls on the courthouse lawn is in the form of a triangular pyramid. Find the height of the pyramid if there are 35 balls in the stack
and each is four inches in diameter."

John didn't say whether or not he will supply the answer to anyone who bogs down, but he has it.

WIRE NEWS
12/23/53

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN RELEASE:

Immediately

MADISON--Research reports and scientific papers by 14 University of Wisconsin scientists are scheduled to be presented as part of the program of the 120th meeting of the American Association for the Advancement of Science, to be held in Boston Dec. 26-31.

The meeting of the association is one of the leading annual scientific events, drawing scientists from all fields and from all parts of the world.

Those from the University of Wisconsin who will take part in the scientific programs are C. R. Bryan, genetics; Robert E. Duncan, botany; Walton C. Galinat, agronomy; J. A. Hayashi, agriculture; M. R. Irwin, genetics; Rudolph E. Langer, mathematics; Karl P. Link, biochemistry; Lilia Martinez-Pico, botany; W. J. Miller, genetics; James M. Naylor, botany; Klaus Patau, botany; Robert E. Parks Jr., Enzyme Institute; W. H. Stone, genetics, and Clinton N. Woolsey, medical school.

####

Complement Suit KARL PAUL LINK
201 Biochemistry Bidg.
Madison, Wisconsin

March 9, 1953

Dr. William H. Bayliss Department of Clinical Research Hoffmann-LaRoche, Inc. Nutley 10, New Jersey

Dear Dr. Bayliss:

Re: Summary of Karl Paul Link for Professor Th. Koller of Basle, President of the pending International Thrombosis Congress.

Your letter of 2/11/53 to the Director of Public Relations of the University has been referred to me for reply. This makes me part of a conspiracy "to get my horn blown". Accordingly I will blow briefly.

1. Scientific career, etc.

Karl Paul Link was born at LaPorte, Indiana, January 31, 1901. He received the degrees of B.Sc. (1922); M.Sc. (1923); and Ph.D. (1925) in Agricultural Chemistry at the University of Wisconsin, Wadison, Wisconsin.

Under the auspices of the International Education Board 1925-27, he studied carbohydrate chemistry at the University of St. Andrews, Scotland with the late Sir James Irvine F.E.S., K.B.E.; micro-chemistry at the Institute for Medical Chemistry Graz, Austria with the late Prof. Dr. Fritz. Pregl, (Nobel laureate); and organic chemistry at the University of Zurich, Switzerland with Prof. Dr. Paul Karrer (Nobel laureate).

He returned to his Alma Mater in 1928 and since 1931 he has been Professor of Biochemistry at the University of Wisconsin.

2. Prizes and distinctions, etc.

Honorary member of the Harvey Society (New York City), member National Academy of Sciences (Washington D. C.; awarded the Cameron Prize in Practical Therapeutics for 1952 by the Faculty of Medicine, University of Edinburgh, Scotland.

3. Important publications, stc.

His fields of research have been carbohydrate chemistry, disease resistance in plants, the chemistry of the 4-hydroxy-coumarins, and the biochemistry and physiology of blood coagulation.

His laboratory established the etiology of the hemorrhagic sweet clover disease of cattle by the isolation, identification and synthesis of Dicumarol (3,3'-methylenebis(4-hydroxycoumarin), and made Dicumarol available for clinical use.

His laboratory also discovered and developed the anticoagulant rodenticide warfarin 3(a-acetonylbenzyl)-4-hydroxycoumarin.

His laboratory was the first to show that the hypoprothrombinemia induced by the 4-hydroxycoumarin anticoagulants can be reversed by vitamin K compounds, and thus supplied the medical profession with the basic practical method for the control of the 4-hydroxycoumarin anticoagulants (Dicumarol, cyclocumarol, tromexan, and warfarin:sodium derivative) in their clinical use.

Cordially yours,

Karl Paul Link

Professor of Biochemistry

KPL:kff

HOFFMANN-LAROCHE INC.

PHARMACEUTICALS AND VITAMINS . ROCHE PARK . NUTLEY 10 . NEW JERSEY . NUTLEY 2-5000

February 11, 1953

Director of Public Relations University of Wisconsin Madison, Wisconsin

Gentlemen:

Our associates in Basle, Switzerland have been asked by Professor Th. Koller of Basle to supply him with a short summary of the scientific activities of the men who will speak at the International Thrombosis Congress to be held shortly in Basle. Dr. Koller is the president of the congress and the summaries are intended for program use.

Since Dr. Karl P. Link, Professor of Biochemistry, is to lecture at the congress, we are writing to ask your help in supplying the following information concerning him:

- 1 His scientific career and the important men with whom he has been associated
- 2 Titles, prizes and distinctions which have been bestowed upon him
- 3 His important publications in the field of thrombosis and related subjects, and whether these are concerned with the physiological or pathological clinical aspects of blood coagulation
- 4 Any new concepts or techniques on which he is working which can be made public

We would appreciate your help and look forward to hearing from you.

Sincerely.

William H. Bayliss

Department of Clinical Research

WHB:cb

The University of California

Biochemistry and Virus

Laboratory Staffs

Karl Paul Link

cordially invite you to attend

THE OPENING CEREMONIES OF THE BIOCHEMISTRY AND VIRUS LABORATORY BUILDING

On the Berkeley Campus of the University of California



OCTOBER 9, 10, 11 1952

PRELIMINARY PROGRAM THURSDAY, OCTOBER 9, 1952

1:00-4:30 p.m. REGISTRATION

South Lobby, Ground Floor, Biochemistry and Virus Laboratory

2:00-4:00 p.m. OPEN HOUSE AND CONDUCTED TOURS

Tours start from South Lobby, Ground Floor, Biochemistry and Virus Laboratory

4:30 p.m.

OPENING CEREMONIES for the Emil Fischer Library and Observance of the One Hundredth Anniversary of the Birth of Emil Fischer. Emil Fischer Library, Fourth Floor, Biochemistry and Virus Laboratory

SPEAKERS:

VINCENT DU VIGNEAUD, Professor of Biochemistry and Chairman of the Department, Cornell University Medical College, New York

H. O. L. FISCHER, Professor of Biochemistry, University of California

WENDELL M. STANLEY, Professor of Biochemistry, Chairman of the Department and Director of the Virus Laboratory, University of California

FRIDAY, OCTOBER 10, 1952

9:15 a.m.

SYMPOSIUM ON BIOCHEMISTRY AND VIRUSES

International House Auditorium Chairman: Wendell M. Stanley

Welcoming Remarks—CLARK KERR, Chancellor of the University of California at Berkeley

Biochemistry and Medicine—Wendell Griffiths, Professor of Physiological Chemistry, School of Medicine, University of California Medical Center, Los Angeles

Some Aspects of Plant Biochemistry—Karl Paul Link, Professor of Biochemistry, University of Wisconsin, Madison

Protein Hormones with Special Reference to Hormones of the Posterior Pituitary Gland— VINCENT DU VIGNEAUD, Professor of Biochemistry, Cornell University Medical College, New York

Molecular Biology—Detlev W. Bronk, President of the National Academy of Sciences, Washington, D.C., and of Johns Hopkins University, Baltimore

Amino Acid Requirements of Man—WILLIAM C. Rose, Professor of Biochemistry, University of Illinois, Urbana

FRIDAY, OCTOBER 10, 1952

12:30 p.m.

LUNCHEON—Reservations required

CONTINUATION OF THE SYMPOSIUM on Biochemistry and Viruses. International House Auditorium

2:00 p.m.

Contributions of Plant Virus Research—LOUIS
O. Kunkel, Member Emeritus of the Rockefeller Institute for Medical Research, New
York

Trends in Research on Poliomyelitis and other Viruses—Thomas M. Rivers, Director of the Hospital of the Rockefeller Institute for Medical Research, New York

Virus Diseases as a Public Health Problem— MALCOLM MERRILL, Deputy Director and Chief, Division of Laboratories, California State Department of Health, Berkeley

Virus Vaccines and Human Welfare—HERALD Cox, Director of Virus and Rickettsial Research, Lederle Laboratories Division, American Cyanamid Company, Pearl River

Vectors and Reservoirs of Virus Diseases— K. F. Meyer, Director of the Hooper Foundation, University of California School of Medicine, San Francisco

FRIDAY, OCTOBER 10, 1952

7:00 p.m.

BANQUET (Informal) — Reservations required, Claremont Hotel, Berkelev

Toastmaster—Robert Gordon Sproul, President of the University of California

Greetings—Detley W. Bronk, President of the National Academy of Sciences, Washington, D.C.

Address—Alan Waterman, Director of the National Science Foundation, Washington, D.C.

Address—Sir MacFarlane Burnet, Director of the Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne Australia

SATURDAY, OCTOBER 11, 1952*

9:00-11:45 a.m. OPEN HOUSE AND CONDUCTED TOURS Tours start from South Lobby, Ground Floor, Biochemistry and Virus Laboratory

* Pacific Slope Biochemical Conference will be held in the Lecture Room at the South End, Ground Floor of the Biochemistry and Virus Laboratory on this day

INFORMATION

In order to permit proper arrangements to be made, it would be greatly appreciated if you will fill out the enclosed card if you expect to attend and return it at your earliest convenience. Those returning the card will receive information regarding hotels and points of interest in the Bay Area, luncheon and banquet reservation blanks, and final programs for the Opening Ceremonies of the Biochemistry and Virus Laboratory Building and for the Pacific Slope Biochemical Conference.

VIRENEWS
FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

RELEASE:

9/16/52

Immediately

MADISON-Karl Paul Link, the University of Wisconsin's famed biochemist, has been selected to speak at the dedication ceremonies of the University of California's new Biochemistry and Virus Laboratory, to be held October 9-11 at Berkeley.

Prof. Link will take part in a symposium on biochemistry and viruses. Among the other speakers on the symposium are Detlev Bronk, president of the National Academy of Sciences; Thomas M. Rivers, director of the hospital of the Rockefeller Institute for Medical Research, New York; Herald Cox, director of virus research for the Lederle Laboratories, New York; and K. F. Meyer, director of the Hooper Foundation of the University of California School of Medicine.

The title of Prof. Link's address is "Some Aspects of Plant Biochemistry."

U.W. NEWS

6/19/52

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6. WISCONSIN

RELEASE:

Immediately

MADISON, Wis.—University of Wisconsin regents voted Thursday to censure one of the University's prominent scientists, Dr. Karl Paul Link, for "making unwarranted accusations...unfair to the individuals concerned and detrimental to the University."

Dr. Link, in whose laboratories dicumarol and warfarin were discovered, had charged that University administrators failed to co-operate with him in research on calf scours, forcing him to take the project out of the state.

"It is the opinion of the regents that the charges made by Dr. Link were without any foundation whatsoever," the regent statement, drawn up by a special committee, declared. Regent Wilbur Renk, Sun Prairie, was chairman of the committee which investigated the charges, and members included Dr. R. G. Arveson, Frederic; Leonard J. Kleczka, Milwaukee, and F. J. Sensenbrenner, Neenah, exofficio.

The statement praised Link's "great ability as a scientist," and said that over the years he "has been given as generous support in his research work as has been possible with the available funds and facilities."

His discoveries, the regents said, have been "of immeasurable benefit to mankind."

But the statement added:

"The Board of Regents expects a member of the University staff to submit any complaints alleging improper personal treatment by the University in a proper and timely manner through administrative channels, even to the regents if need

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ad one-Link

be, before airing such criticisms publicly."

The full text of the regent statement follows:

The regents of the University have investigated the facts relating to recent charges publicly made by Dr. Karl Paul Link against Dr. E. B. Fred, Dr. I. L. Badhwin and Dr. C. A. Elvehjem in connection with the research conducted by him on calf scours. It is the opinion of the regents that the charges made by Dr. Link were without any foundation whatsoever. The making of such unwarranted accusations is unfair to the individuals concerned and detrimental to the University; and Dr. Link is subject to censure for having broadcast such unwarranted charges.

"Dr. Link over the years has been given as generous support in his research work as has been possible with the available funds and facilities. His great ability as a scientist has resulted in his research being very productive and has resulted in discoveries of immeasurable benefit to mankind. Dr. Link and all other members of the University of Wisconsin staff have enjoyed wide freedom in planning and carrying on their research including the freedom to conduct their research off the campus or outside of the State of Wisconsin and including the freedom to pursue a particular line of approach towards the solution of a problem irrespective of the fact that another member of the staff might deem a different approach to be more desirable. In accordance with these freedoms, which have been traditionally maintained at the University of Wisconsin, Dr. Link was able to conduct experiments relating to calf scours outside of the State of Wisconsin without obtaining the written permission of University administrators and the University administrators were not derelict in carrying out their administrative functions by not directing that the efforts of other staff members be diverted from their own lines of approach to a solution of this problem to that which was being pursued by Dr. Link.

"The Board of Regents expects a member of the University staff to submit any complaints alleging improper personal treatment by the University in proper and timely manner through administrative channels, even to the regents if need be, before airing such criticisms publicly."

REPORT OF THE SPECIAL REGENT COMMITTEE ON PERSONNEL ITEM TO THE BOARD OF REGENTS

June 19, 1952

The Special Regent Committee appointed to give further consideration to, and to report informally to the Board on, the personnel matters regarding Dr. Karl Paul Link submits the following report to the Board with the recommendation that it be adopted:

The Regents of the University have investigated the facts relating to recent charges publicly made by Dr. Karl Paul Link against Dr. E. B. Fred, Dr. I. L. Baldwin and Dr. C. A. Elvehjem in connection with the research conducted by him on calf scours. It is the opinion of the Regents that the charges made by Dr. Link were without any foundation whatsoever. The making of such unwarranted accusations is unfair to the individuals concerned and detrimental to the University; and Dr. Link is subject to censure for having broadcast such unwarranted charges.

Dr. Link over the years has been given as generous support in his research work as has been possible with the available funds and facilities. His great ability as a scientist has resulted in his research being very productive and has resulted in discoveries of immeasurable benefit to mankind. Dr. Link and all other members of the University of Wisconsin staff have enjoyed wide freedom in planning and carrying on their research including the freedom to conduct their research off the campus or outside of the State of Wisconsin and including the freedom to pursue a particular line of approach towards the solution of a problem irrespective of the fact that another member of the staff might deem a different approach to be more desirable. In accordance with these freedoms, which have been traditionally maintained at the University of Wisconsin, Dr. Link was able to conduct experiments relating to calf scours outside of the State of Wisconsin without obtaining the written permission of University administrators and the University

administrators were not derelict in carrying out their administrative functions by not directing that the efforts of other staff members be diverted from their own lines of approach to a solution of this problem to that which was being pursued by Dr. Link.

The Board of Regents expects a member of the University staff to submit any complaints alleging improper personal treatment by the University in proper and timely manner through administrative channels, even to the Regents if need be, before airing such criticisms publicly.

U.W. NEWS

2/22/52

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN RELEASE:

TO

Medison, Mis. — A national pat on the back for University of Wisconsin Biochemist Karl Paul Link and the wonder rat-killer warferin, which was developed in the University's biochemistry laboratories is published in the March issue of Reeders Digest, which hit the newsstands Wednesday.

Authored by Paul de Eruif, the article labels rate the "deadliest, most destructive of all animal anemies of humanity," and points out that man never has been able to win the fight against rate.

"But now," do Kraif declares, "Dr. Karl Paul Link of the University
of Misconsin has cooked up a curious chemical poison called warfarin, which
can seal the rodent's doom."

Soting that the new poison works slowly and makes the rate bleed to death intervally, do Eruif points out that for the first time a rat-killer has been discovered which does not make the rate bait-shy.

The author traces the development of the new lethel poison through its first scenin Diesmarsh, amother University of Misconsin discovery, used extensively in medicine to prevent the cletting of blood. Further research led to "composed bi," do Kredf research, which "was a bust as a clot preventer compared to Diesmarsh," but expect to bleed to death internally mithout their realising it much more effectively than Diesmarsh. Compound by eventually became memberia.

De Kruif recounts how Link tested the poison on chickens and found it did not harm them, and that it had no effect on people who ate chickens which had eaten the poison. He tells extensive experimental tests which resulted in complete control of the ret problem on close to 90 per cent of all premises, and says that the few failures were caused by the type of bait used.

"Warfarin is safe to domestic animals, pets, and children," de Kruif reports. "No case of human poisoning has been reported, not a single case of poisoning of domestic animals proved. This is explained by the extremely low concentration of warfarin in the bait, one part in 4,000, and by the fact that one dose doesn't kill; warfarin has to be eaten on many days to doom any animal."

U.W. NEWS
FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

3/16/51

RELEASE:

Madison, Wis .-- Recent releases and publications from the University of Wisconsin News service about the discovery of the chemical compound now known as warfarin, potent new rat poison, have been incomplete in that they did not point out that the invention of the new chemical compound was a joint invention, the News service said last night.

The U. S. patent was granted in 1947 to Mark A. Stahmann, Miyoshi Ikawa, and Karl Paul Link, after its discovery in U. W. laboratories.

Stahmann and Link are members of the U. W. biochemistry faculty.

Ikawa is now a member of the staff of the California Institute of Technology.

The patent is being administered by the Wisconsin Alumni Research foundation.

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

2/21/51

RELEASE:

Madison, Wis .- A national pat on the back for University of Wisconsin Biochemist Karl Paul Link and the wonder rat-killer warfarin, which was developed in the University's biochemistry laboratories is published in the March issue of Readers Digest, which hit the newsstands Wednesday.

Authored by Paul de Kruif, the article labels rats the "deadliest, most destructive of all animal anemies of humanity," and points out that man never has been able to win the fight against rats.

"But now," de Kruif declares, "Dr. Karl Paul Link of the University of Wisconsin has cooked up a curious chemical poison called warfarin, which can seal the rodent's doom."

Noting that the new poison works slowly and makes the rats bleed to death internally, de Kruif points out that for the first time a rat-killer has been discovered which does not make the rats bait-shy.

The author traces the development of the new lethal poison through its first cousin Dicumarol, another University of Wisconsin discovery, used extensively in medicine to prevent the clotting of blood. Further research led to "compound 42," de Kruif recounts, which "was a bust as a clot preventer compared to Dicumarol," but caused rats to bleed to death internally without their realizing it much more effectively than Dicumarol. Compound 42 eventually became warfarin.

De Kruif recounts how Link tested the poison on chickens and found it did not harm them, and that it had no effect on people who ate chickens which had eaten the poison. He tells extensive experimental tests which resulted in complete control of the rat problem on close to 90 per cent of all premises, and says that the few failures were caused by the type of bait used.

"Warfarin is safe to domestic animals, pets, and children," de Kruif reports. "No case of human poisoning has been reported, not a single case of poisoning of domestic animals proved. This is explained by the extremely low concentration of warfarin in the bait, one part in 4,000, and by the fact that one dose doesn't kill; warfarin has to be eaten on many days to doom any animal."

The discoverer of Dicumarol and Warfarin has been a familiar figure on the campus since 1918, when he came to Madison from his La Porte, Ind., home to work his way through the University. He holds three UW degrees: B.S., 1922, M.S., 1923; and Ph.D., 1925; and he has studied abroad at the Universities of St. Andrews, Scotland; Graz, Austria; and Zurich, Switzerland. Since 1931 he has been UW professor of biochemistry. Because two veterinarians years ago a sked Dr. Link why cows were bleeding to death, he started a detective process which resulted in the drug which prevents blood-clotting and annually saves lives threatened by strokes, heart attacks, apoplexy, and gangrene. His latest discovery, Warfarin, promises to be the most effective rat poison yet invented.

RENEWS FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN 4/26/49

RELEASE:

Immediately

K. P. Link

Dr. Samuel M. McElvain, professor of chemistry at the University of Wisconsin. was elected a member of the National Academy of Sciences at a meeting of the academy in Washington Tuesday. Election to the academy is a recognition of unusual ability and carries with it an obligation to the government. Only 30 men may be elected to membership at each annual meeting.

Dr. McElvain came to the University of Wisconsin in 1923 after receiving his Ph.D. at the University of Illinois. His special field is organic chemistry. He is a member of the American Chemical society, the British Chemical society, and Sigma Xi, the foremost general science society.

The University of Wisconsin ranked second among state universities in the number of members in the academy before Tuesday's election. Only nine universities in the country had more members than Wisconsin.

Twelve University of Wisconsin men previously honored by membership are: President Edwin B. Fred; Conrad A. Elvehjem. dean of the Graduate School and chairman of the biochemistry department; Charles E. Allen, emeritus professor of botany; Edwin B. Hart, emeritus professor of biochemistry; Walter J. Meek, emeritus dean of the Medical

school; Joel Stebbins, emeritus professor of astronomy; Charles K.

Leith, emeritus professor of geology; Homer Adkins, professor of chemistry; Royal A. Brink, professor of genetics; Farrington Daniels, professor of chemistry; Karl P. Link, professor of biochemistry; and

John C. Walker, professor of plant pathology.

The academy serves as scientific adviser to the government on problems of science and applied science. From it any department may seek unbiased, expert aid. As a result, membership is restricted largely to scientists who have made major contributions to knowledge and are in a position, upon request, to serve the government in the solution of its problems in science.

Madison, Wis. (Special) -- University of Wisconsin discoverers of the drug dicumarol, an aid for failing hearts, are given recognition in the "Medical Front" section of the May issue of Science Illustrated, now on news-stands.

"The newest treatment for coronary thrombosis uses dicumarol, an anti-clotting drug," the article states. "It is not new, having been first synthesized in 1940. But it has only recently taken its place in the medical arsenal. Dr. Karl Paul Link, professor of biochemistry at the Wisconsin Agricultural Experiment State, put the final stamp of approval on dicumarol recently at an American Chemical Society meeting in Cambridge, Mass."

Coronary thrombosis is the heart "attack" caused by lodgement of a blood clot in the arteries which feed certain heart muscles.

Dicumarol was discovered in the late 1930's by Link and his co-workers who found it in sour clover hay which induced fatal hemorrhages in cattle. Its anti-clotting capacity has been turned to good use in medicine.

"Administered in resonable doses," the article adds, "it reduces the blood's clotting tendencies only slightly, just enough to prevent internal clot formation."

Heparin is the drug formerly used for this purpose, but dicumarol is cheaper and can be administered by mouth while heparin must be injected. Dicumarol is also useful in treating other diseases caused by clotting.

a Look at the Future

The colleges and universities of America are confronted with a problem which was foreseen by few, if any of them. The problem relates to the numbers of students desiring college education. The immediate increase is due to the enrollment of veterans but all indicati point to a large and steady permanent growth.

In 1940 American colleges and universities enrolled about 1,250,-100 students and this was close to the maximum which could be accommodated. It is now quite certain that over 2,000,000 students will apply for admission to our colleges and universities in the fall of 1946, and that with the most effectively improvised accommodations shat can be arranged, approximately 200,000 to 400,000 of them jannot be accommodated.

The tremendous increase in enrollment is not a temporary bulge. Available evidence indicates that college enrollments may double between 1940 and 1946. Increasing numbers of returned veterans will swell the numbers for the next 10 years. Quite apart from the veterans there has been a steady increase in the percentage of high school graduates attending college. In recent years this gain in number of high ates attending college. In recent years this gain in number of high school graduates entering colleges has been much greater than was anticipated. For example, the number of high school graduates entering the University from Wisconsin high schools has practically doubled between 1940 and 1946. In the nation by 1960, though the number of veterans attending college will be small, the number of high school gradwates will probably be sufficient to maintain the attendance total of 3,000,000. This compares with about 1,500,000 in 1940. It is realized, of course, that economic reverses, might reduce college attendance in any period in which such reverses occur. The long-time trend however, seems to be written, even though it is modified by economic conditions in certain years. nomic conditions in certain years.

It now seems that in the State of Wisconsin the existing uni-

versities and colleges can, by extending their facilities to the maximum, accommodate about 44,000 students in 1946-47. Present indications are that upwards of 48,000 will wish to enroll this year.

A large number of qualified Wisconsin boys and girls will not find it possible to gain admission to any college.

Projecting present trends as accurately as possible, it seems reason.

able to predict that the colleges and universities of the state will need to consider in the immediate future and the long run an enrollment of about 60,000 students. During each year of the decade 1950-60 the number who will demand college education will vary from 55,000,-60,000. the will have to be increased by 40 per cent over this year's facilities within the next 5 to 15 years.

and of the state-wide situation, the immediate problem for the University in the three years ahead is revealed in the rollowing

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T,	NROLLMENT ESTIM	AILD,	FALL 1946,	1947, and 194	łÖ
		1946	1947	1948	
	Seniors	. 1,800	2,500	4,000	
	Juniors	2,800	4,500	5,500	
	Sophomores	4,500	6,000	6,000	
	Freshmen	5,000	4,250	6,000	
	Graduates	1,750	2,000	2,200	-
	Law and Medicine	650	750	800	
	Totals	16.500	20.000	22,500	

The figures are believed to be conservative, but they pointedly in The figures are believed to be conservative, but they pointedly indicate an extremely critical situation which requires drastic action if the State of Wisconsin is to attempt to meet the problem which it now faces and which will be tragic if bold steps are not taken to meet it by the fall of 1947. Unless the University can solve the problem of oviding housing and instructional facilities for more than 16,500 stuve, it would be faced with disastrous necessity of limiting its freshman of 600 in 1947 and 1,000 in 1948 or of dismissing qualified

already enrolled.

e State educational institutions are to admit the number of who will be qualified to enter college and who will want of Wisconsin institutions and also provide facilities for or wisconsin institutions and also provide racinities for school who are qualified to continue, immediate steps to provide housing and educational facilities at Madi-500 additional students by September, 1947. The nea who intend to enroll this month is 4,180. The en desiring to enroll in September of 1947 will

umber. Can we prepare housing and instruc
we begin now? Obviously there is no time

> y can solve only a part of the problem ay plan through the University at of students in 1947-48 and possi-University does so, it seems cer-ity of the state to offer college bart.

rion are inadequate. Present rire requirements. It seems not at Madison must be ade aware of the oppor-University has an vith the other educahave been raised

sity next v small ersity

From Cattle Disease to Valued Lifesaver Came Drug Dicumarol With Aid of U. W. Scientists

It is another of the strange stories of scientific research that the drug dicumarol, first identified as the mysterious agent which caused the death of whole herds of cattle from the "sweet clover disease," should become one of the most challenging recent developments in the field of medicine and surgery.

For this drug—which is now saving innumerable human lives from the hazard of post-operative clotting within the blood vessels—first became known to scientists for its effect on cattle, as the "sweet clover disease" with which farmers of the Midwest have long had bitter acquaintance.

It remained for scientists at the

had bitter acquaintance.

It remained for scientists at the University of Wisconsin working under the direction of Dr. Karlaul Link, of the agricultural experiment station, not only to discover the cause of the disease of cattle but also to find one of the world's great anti-coagulants—of which there are now only two at the disposal of surgeons.

It is another of those great stories which dot the annals of American science, and it might be said to have begun in earnest in 1932 when Dr. Link's assistant, Dr. Harold Campbell, drove to a small farm near Westfield, Wisconsin.

The farmer's herd had the sweet clover disease—induced by feeding improperly cured clover hay. Of the herd of 20 already four had died in typical fashion: profuse bleeding through even the smallest scratch, for the blood had lost its power to clot.

Previous work by other agricultural scientists had shown that only animals fed on clover hay contracted the disease, and, strangely enough, that a change to an alfalfa diet restored the coagulating power of the blood.

Dr. Link and Dr. Campbell saved the farmer's herd with a butter-like extract from alfalfa—and began seven year's research to the more or lates settled back to the more or lates.

and began seven year's research into the chemical and biological nature of the substances involved, research which has resulted in discovery of the medical value of dicumarol.

dicumarol. They isolated and purified the white crystalline drug; but what, they asked, was the agent in the alfalfa extract which had acted so effectively as an antidote—a vital piece of information before the drug could be safely administered to humans, for without a counteractant at hand it might induce a hemorrhage just as dangerous as the embolism which results from the embolism which results from the blood forming a clot within a major blood vessel.

It seemed that the agent in alfalfa might be one of the known vitamins—vitamin K, found in all leafy vegetables such as spinach, lettuce, and alfalfa. Months of experimentation in the laboratories at the University of Wisconsin were inconclusive. It began to appear that something other than vitamin K must be responsible. But none could be found. Yet, under extensive testing, the doses of vitamin K given to experiment—

of vitamin K given to experiment-al rabbits and dogs failed to re-store the coagulating power of the blood which had been destroyed

periencing an upsurge which parallels that which followed World War I. The return of the veterans is markedly accentuating a trend which, barring unforeseen national circumstances, will boost college enrollments to double their pre-war size during the first twelve to fitteen years.

3. Shall the University roise its admissions requirements in order to the the treatment of the statements.

to further restrict enrollments?

Colleges have a moral obligation, under present circumstances, not make full use of callege opportunities to use space which would be

make rull use of catego opportunities to use space which reduced better by students of higher promise.

It is believed, however, that an arbitrary boosting of admission requirements which would disqualify students who otherwise would have qualified for admission, would be both unfortunate and unwise. It is doubted that a restriction of educational opportunity of capable young men and women is a wise social policy.

4. Shall the University further restrict the enrollment of non-resi-

aent students.

Since January 15, the University has suspended, with rare exceptions made in individual cases, the admission of non-resident applicants to all undergraduate schools and colleges. All former students, however, have been permitted to return regardless of their residence. The Gradustic School has been been permitted to return regardless of their residence. ate School has had no restriction upon non-resident students, but has raised its admission requirements for all applicants, resident and nonresident. These graduate students are needed to help as teachers and to provide the staff that will be desperately needed in the near future.

The University of Wisconsin has annually attracted students from practically every state in the United States. Normally, this is a healthy situation and much to be desired. It is doubted that the University could

stuation and much to be desired. It is doubted that the University could wisely refuse to allow non-resident students, patituality veterans, to return and complete educational careers which they had begun before their entrance into the armed services.

(Excerpt from Minutes of Faculty Meeting—January 7, 1946: "III. That the Faculty feels that the above measures insofar as they diminish opportunity for out-of-state students to attend the University, tend in an unhappy fashion to deprive Wisconsin's own young men and women of the educational values which derive from broadly international resumbaness.

tional personal acquaintanceships on the campus.")

5. Shall the University expand its program of extension centers?

It is clear that every type of educational plan and facility will have to be used to insure the veterans and other young men and women of Wis-consin a college opportunity in the state. The present facilities, both-pri-vate and public, cannot be expanded either rapidly enough or sufficiently to care for the load expected in the next blennium. The expansion of the

extension center program appears inevitable.

6. What is the solution for this dilemma?

It would be absured and presumptious for the University to assume that it can solve the problem or that it alone knows the answer. The problem is larger than any single institution, or group of institutions. Public policy is involved. At present it seems that requests for appropriations for the coming biennium should be based upon needs of a student body of 20,000 in 1947-48 and 22,500 in 1948-49. A more accurate estimates the coming biennium should be the seed upon needs of a student body of 20,000 in 1947-48 and 22,500 in 1948-49. A more accurate estimates the comment of the comment

mate can be prepared in about Z weeks, following registration.

Also other developments will be pointed up more definitely in two or three weeks when the colleges of the state will have opened. Enrollment figures can then be compared with predicted figures and future

ment figures can then be compared wan proment figures can then be compared wan proceeds will be more certain.

When the returns are in, appropriate representatives of the Regents of the Teachers Colleges and of the Regents of the University should confer and determine upon a procedure by which the Boards of Regents, the presidents of the Teachers Colleges and the administrative committee of the University should be brought into conference to discuss the most advisable program to meet obvious needs. Educational statesmanship is demanded.

EDWIN B. FRED, President University of Wisconsin

Having all but given up their attempt to find the solution to this problem, Dr. Link and his associates settled back to the more or less academic work with which all scientists concern themselves when confronted with a new chemical compound—they began the unexciting job of finding the chemical structure of the complex dicumarol. chemical s dicumarol

What they uncovered made them scratch their heads—and glance again at that bottle of vita— min K which had been gathering months of dust on their labora-tory, shelf. Surprisingly enough, the chemical structure of dicumarol was similar to that of vitamin K-too similar for chance to play a part.

And they remembered that un-written medical law which said similar chemical compounds fre-quently have nearly opposite physiological effects.

Back the scientists went to their rabbits and their dogs, ad-ministering small doses of the vitamin—and, later, huge doses. There they found the secret. Vita-min K would act as an antidote, would restore coagulating power to dicumand-thinned blood, only in huge, but harmless doses.

to dicumarol-thinned blood, only in huge, but harmless doses.

And them—from a major discovery of veterinarian science—dicumarol found its place in surgical medicine. Wasn't it possible, scientists asked, to use dicumarol in the operating rooms!

Wasn't if possible, they asked, that this drug which caused the serious hemmorhagic disease in cattle might be used to a purpose in surgery—to prevent dangerous blood clots from forming in the veins and arteries after an operation! And condin't it be controlled now that vitamin is had been found to be an antidote; controlled so that a patient given dicumarol to break up a clot would not be in equal danger from the possibility of hemorrhage?

The medical men said yes. The Mayo clinic of Rochester, Minnesota, published a report on their post-operative use of the new drug for the prevention of thrombosis and embolism. "In the entire series of 1,000 cases there was only one death from pulmonary embolism, and in this case, which was early in the study, the embolism occurred after the prothrombin had returned to normal."

In other words—after the effect of dicumarol had worn off.

In other words—after the of dicumarol had worn off.

Dicumarol is now widely given as a blood clot preventative agent, and the period of convalescence for patients with thrombic tendencies, and those afflicted with thrombosis, is slashed to fractions. The Mayo clinic also reported that large doses of vitamin K, given to patients exhibiting hemorrhage tendencies after the administration of dicumarol, quickly corrected the balance and made further administration of dicumarol safe. It was this agent—vitamin K—and the hunch of the Wisconsin scientists that its similarity with the structure of dicumarol indicated something more than their experiments proved, that has made the drug one of mankinds' most valued surgical aids.

In the words of one of the doctors at the Injuersity of Wiscon-

In the words of one of the docin the words of one of wiscon-sin who did early work on the drug: "Dicumarol can be prepared drug: "Dicumarol can be prepared in large quantities, cheaply, and can be administered by mouth, while the other anti-coagulant, heparin, is expensive and must be given by injection. Dicumarol is a drug that very successfully prevents blood clotting.
"More over," he continued, "there is little doubt now, from thousands of cases treated over the world, that dicumarol has a real place in the treatment and prevention of clot formation in hemans."

And so it has gone down in the annuals of American science it a drug, first discovered as causative agent in a serious dease of cattle, should become of the great aids to the surgethrough the work of scientists the University of Wisconsin.

FACULTY INFORMATION SHEET University News Service The University of Wisconsin

Info. from Who's Who.

NAME_ Karl Paul Link
POSITION (academic rank, department, date of appointment, etc.)
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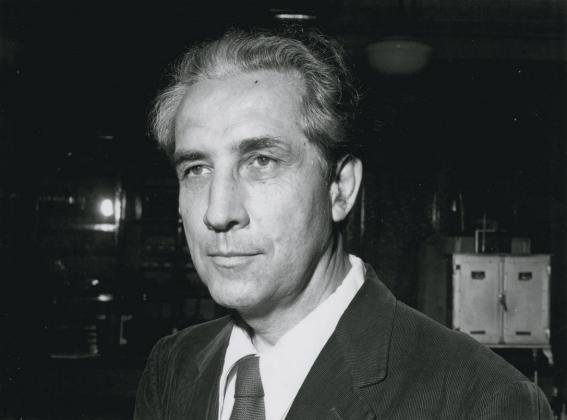
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IN ADDITION TO THE ABOVE "WHO'S WHO" TYPE INFORMATION, WE WOULD APPRECIATE A FEW INFORMAL NOTES ON THE CLASSES YOU TEACH, YOUR HOBBIES, YOUR SERVICE OR WAR WORK, YOUR PUBLIC SERVICE, ETC.

(please use reverse side of these pages for additional information)



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UNIVERSITY OF WISCONSING Extension Division DEPT, OF PHOTOGRAPHS Madison, Wisconsing

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Karl Paul Link

UNIVERSITY OF WISCONSIN NEWS SERVICE OBSERVATORY HILL OFFICE BUILDING MADISON 6, WISCONSIN

OFFICE OF THE DIRECTOR

Prof. Karl Paul Link

Dr. Karl Paul Link, professor of biochemistry at the University of Wisconsin since 1931 and the first to bear that title at the University, first joined the faculty in 1928.

Born in La Porte, Indiana, Jan. 31, 1901, he is the eighth of 10 children of the Rev. George and Fredericka Link. Link is married to the former Elizabeth Feldman. They have three boys--John, Thomas, and Paul.

Dr. Link holds three degrees from the University of Wisconsin: B.S., 1922; M.S., 1923; and Ph.D., 1925. As a fellow of the International Education Board, he studied abroad at the Universities of St. Andreews, Scotland; Graz, Austria; and the University of Zurich in Switzerland.

The Wisconsin professor recently drew national attention when it was revealed that a product of his research, Warfarin sodium, was used as the anti-coagulant administered to President Eisenhower after his 1955 heart attack.

Dr. Link developed the anti-coagulant as the result of a 1933 incident when a farmer brought a milk can of blood to his laboratories. The blood refused to clot. He attributed the fact to the mysterious sweet clover disease which produced hemorrhages and bleeding to death of cows. In 1940, his laboratories isolated, identified, and symthesized the agent which kept blood from clotting. It was named Dicumarol. His laboratories also discovered and developed the anti-coagulant rodenticide, warfarin, the leading rat killer in the world. Some 140 million pounds of the product, which originates from spoiled sweet clover hay, has used since 1950 in the destruction of rats and mice. In the human body, Warfarin sodium prevents death-dealing blood clots in heart attacks and certain kinds of

circulatory deseases by depressing the blood's ability to clot. It is unique in that it is effective when given orally, intravenously, intramuscularly, or rectally while other anticoagulants are effective only when given orally.

Other research activities include work in the areas of the chemistry of the sugars and sugar acids, the bio-chemistry of disease resistance in plants, and immuno foods for the newly born mammal (calves-infants).

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In 1955, Dr. Link was granted one of the Lasker Awards by the American Public Health Association for his "outstanding achievement in medical research." The awards are considered to be among the nation's highest medical honors.

Dr. Link has contributed various scientific papers to professional journals.

Link, Carl Paul, agrl. chemist; b. LaPorte, Ind., Jan. 31, 1901; s. Rev. George and Fredericka (Mohr) L.; student LaPorte St. John's Lutheran parochial sch., 1905-14; LaPorte High Sch., 1918; B.S., M.S., Ph.D., U. of Wis., 1918-25; student U. of St. Andrews, Fifeshire, Scotland, 1925-26; received microanalyst's certificate, U. of Graz. Austria, 1926; U. of Zurich, Switzerland, 1926-27; m. Elizabeth Feldman, Sept. 20, 1930; three children - John Kailin (18) Thomas Paul (14) Paul Konrad (2). Began as asst. asso. prof. agrl. chemistry. U. of Wis. 1927-30; prof. biochemistry since 1931. Served as consultant, chemistry and tech. plant products, 1933; collaborator, U.S. Dept. of Agr., soy bean lab., 1937-40; Northern Regional lab., Peoria, Ill., 1940-45; cons. to Clinton (Ia.) Foods, Inc., since 1938, and to Pabst Brewery, Milwaukee, Wisconsin, since 1944. Cameron Prize (Edinburgh) 1952. Mem. Harvey Soc. (New York City), (hon.) Nat. Acad. Sci. (Washington, D.C.) A.A.A.S.; Am. Chem. Soc., Fedn, Am. Socs. for Exptl. Biology (biol. chemists sect.). Sigma Xi, Phi Lambda Epsilon. Contbr., scientific papers on chemistry of the sugars, disease resistance of plants, 4-hydroxycoumarins and blood coagulation, etc., to professional jours., 1923-53. Headed team of scientists that developed the drug Dicumarol, a blood anticoagulant used to combat intravascular clotting, thrombosis and pulmonary embolism; developed the anticoagulant Warfarin for rodent control and clinical use. Home: Route 2, Madison 5. Office: Biochemistry Dept., Univ. of Wisconsin, Madison 6, Wis.

Karl Paul Link (Biographical Sketch)

Born January 31, 1901 at La Porte, Indiana, being the eighth of ten children of the Reverend George and Fredericka Link. My father and grandfather Link were Lutheran Pastors. The ten Links of my generation are all alive today—ranging in age from 50 to 68 years.

Preliminary schooling

The first 8 years at the St. Johns Lutheran School; the next 4 years at the La Porte, Indiana High School.

University training

1918-1922 University of Wisconsin, B.S. in Agriculture 1922-1925 University of Wisconsin, M.S. in Agriculture Chemistry and Ph.D. in Agricultural chemistry.

Post-doctorate training

As a fellow of the International Education Board (a division of the General Education Board) I studied at:

- a. University of St. Andrews, St. Andrews, Scotland (1925-26)
- b. University of Graz, Graz, Austria (1926)
- c. University of Zurich, Zurich, Switzerland (1926-27)

Academic Career

I returned to the University of Wisconsin in September, 1927 as Assistant Professor of Agricultural Chemistry and was made Professor of Biochemistry in 1930, being the first chemist to bear that title at Wisconsin.

Research activities

I have conducted research in the following general fields:

- a. The chemistry of the sugars and sugar acids
 - b. The bio-chemistry of Disease Resistance in plants
 - c. The chemistry and bio-chemistry of the Coumarins (Dicumarol and the like)
 - d. Immuno foods for the newly born mammal (calves-infants)

Since the Lasker award is in recognition of your "achievements in the study and development of anti coagulants" I propose to give only an account of this work.

(I am omitting the names of my many collaborators—some 20-25 graduate research assistants who have worked with me.)

The development of Dicumarol and other coumarin anti coagulants

Work on the cause of the memorrhagic sweet clover disease of cattle was started in 1933.

Prior to our work, veterinarians in North Dakota and Canada had shown the following:

- a. That when the common varities of sweet clover are made into hay and if this hay is not properly cured it causes (in cattle) the development of spontaneous hemorrhages which can be fatal.
- b. They also showed that withdrawal of the spoiled hay leads to spontaneous recovery and that the basic characteristics of the disease was a loss in the clotting power of the blood. This was shown to be due to the absence of the blood protein Prothrombin, an essential clotting component. *

Isolation - identification - and synthesis of the causative agent of the Hemmorrhagic sweet clover disease of cattle

Between 1933 - April 1, 1940, it was shown by my laboratory:

- 1. That when hay undergoes spoilage the Coumarin content is involved and that the Coumarin molecule is transformed.
 - Note: Coumarin itself is not toxic. It gives newly mown hay its sweet aroma. It is used to scent cheap tobacco and is a component in artificial vanila used to scent bakery goods and is also a component of many perfumes.
- 2. The transformation product of Commarin is the causative agent of the sweet clover disease.

#Note: The hemorrhagic agent does not cause the blood vessels to rupture. The bleeding is due to a defect in the normal clotting mechanism.

- 3. The chemical structure of the anti coagulant is that of two 4-hydroxy

 Coumarin molecules linked in position 3 via a methylene bridge (see chart page
- 4. The hemorrhagic agent could be synthesized from salicylic acid, the basic component of the widely used aspirin. It was named Dicumarol in 1941.

Among the importan physiological and biochemical properties of Dicumarol are that its anti coagulant action can be stopped (or reversed) by the action of the anti hemorrhagic vitamin known as Vitamin K.

This is a very significant fact - for in the clinical use of Dicumarol and the like, vitamin K can be used as an antidote to over-dosing. Accordingly in clinical practice today actual bleeding caused by over-dosing is a relatively uncommon situation. It should be emphasized that there are very few potent and useful drugs that have a specific antidote - like that which exists in the Dicumarol vitamin K relationship.

(See chart - U.W. photo 9540 - B.)

The action of Dicumarol can be controlled - abolished - or prohibited by vitamin K compounds Menadione or vitamin K and the like.

The most potent inhibitor is vitamin K₁ the naturally occurring form that occurs in most green plant tissue - like good alfalfa hay, spinach, onion greens, etc.

Vitamin C (ascorbic acid) also influences the action of Dicumarol acid like anti coagulants. The effect of vitamin C is indirect and still obscure. Vitamin C is necessary for the maintenance of the integrity of the capillary wall - which in turn is necessary for the normal circulatory processes to proceed.

In the absence of vitamin C the capillary bed is more prone to the escape of blood be it normal from the standpoint of its coagulability - or below normal as is the case when Dicumarol is used clinically.

The synthesis of other anti coagulants related in physiological action to the causative agent of the hemorrhagic sweet clover disease (Dicumarol)

After the structure of Dicumarol was established and its synthesis developed, it was an easy matter to make other compounds with a similar action. Among those that

were sorted out from close to 300 kith and kind of Dicumerol. I shall mention only those that have been tested extensively in clinical practice. They are:

Tromexan (See chart)

Cyclocurnarol

The 1-3 indanediones

Warfarin

and

Warfarin Sodium

Today (July 27, 1955) Dicumarol is still the most widely used oral anti coagulant.

Of the others indicated it would appear that Warfarin and Warfarin Sodium have

certain advantages which might lead to a replacement of the clinical use of Dicumarol.

It might be indicated in passing that Warfarin (first made by us in 1942) was

originally promoted for rodenticide purposes (1948) and became available for use in

1950. It is today the most effective, the most widely used and the safest multiple

dose rodenticide known.

Its safety resides in the fact that:

- a. multiple doses are necessary to cause fatal bleeding
- b. in the event of accidental exposure by a child to a single feeding of Warfarin.

 dangerous hemorrhage does not develop.
- c. if the exposure has been multiple, vitamin K is efficient and effective antidote.

The clinical use of Dicumarol and the like

The pioneer clinical trials on the use of this anti coagulant in medicine were made at the Wisconsin General Hospital (0.0. Meyer et al) and the Mayo Clinic, Rochester, Minn. (Butt, Allen, and Bowman) in 1942.

The American Heart Association - Committee on anti-coagulants, 1946-49, (headed by Irving S. Wright, M.D.) has published a 655 page report entitled <u>Myocardial Infarction</u>, Its Glinical Manifestations and Treatment with Anti-coagulants, Grime and Strather publishers, New York City, 1954, based largely on the use of Dicumarol.

circulatory deseases by depressing the blood's ability to clot. It is unique in that it is effective when given orally, intravenously, intramuscularly, or rectally while other anticoagulants are effective only when given orally.

Other research activities include work in the areas of the chemistry of the sugars and sugar acids, the bio-chemistry of disease resistance in plants, and immune foods for the newly born mammal (calves-infants).

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RELEASE:

CUTLINES FOR ACCOMPANYING PICTURE

The University of Wisconsin's Karl Paul Link (right) and Mark Stahmann, working in the laboratories of the biochemistry department.

Dr. Link headed the team of Wisconsin scientists that developed Dicumarol, the drug to combat intravascular clotting, thrombosis, and pulmonary embelism; and he is presently directing the work on Compound 42, a new and more effective chemical for use in the war against rats.

Dr. Link received his Ph.D. from Wisconsin in 1925. Since becoming a member of the faculty in 1927, he has built a brilliant record as biochemist with the University.

#

Prof. Karl Paul Link University of Wisconsin Biochemistry Department University News and Publications University of Wisconsin Madison (608) 262-3571

Biochemist Karl Paul Link has been called at turns a University of Wisconsin genius, stormy petrel, iconoclast, and most colorful character.

But it is true that thousands of people throughout the world owe their lives to the man who discovered dicumarol, the first of the synthetic anti-coagulants, which enabled physicians to combat such disabling and deadly diseases as coronary thrombosis or "heart attack".

Prof. Link also, in the process of his extensive research at the University, developed Warfarin, regarded as the leading rodent poison in all parts of the world, and then, a few years later, developed sodium warfarin, which has almost replaced dicumarol as the synthetic anti-coagulant in the medical battle against coronary thrombosis or heart attack.

His beneficiaries include the late Pres. Eisenhower who had to take the sodium warfarin following his attack in Denver in 1955.

The facts of this life-saving science story, told by Prof. Link himself, go like this:

"Between 1933 and 1940 we were working on the hemorhagic sweet clover disease of cattle.

"The causative agent, a coumarin, was found and named Dicoumarol.

"Between 1940 and 1942 we made many coumarin derivatives that acted in the body like Dicoumarol.

"Between 1942 and 1948 one of these coumarin compounds was studied intensively, and between 1948 and 1950 we concentrated on what became known as Warfarin, which rapidly became the leading rodent control agent throughout the world.

(more)

"Subsequently, its water soluble sodium derivative, sodium warfarin, has become the leading oral anti-coagulant in clinical practice, and it is replacing Dicoumarol."

The University has received millions of dollars from royalties on the sale of his drugs through the Wisconsin Alumni Research Foundation for which Warfarin is named.

Prof. Link has had some strong arguments with UW authorities during his career, has served as adviser to campus liberal organizations always under University rules and regulations, and twice has been a patient in a tuberculosis sanitorium.

His international honors have been many, including the Cameron Award given by the madical faculty of the University of Edinburgh, Scotland, in 1952; the coveted Albert Lasker Award of the American Public Health Association, in 1955; the John Scott Award from the City of Philadelphia, in 1959; and in 1967 he was presented with the National Academy of Science Jessie Stevenson Kovalenko gold medal award for his pioneering work in anti-coagulants.

He is a member of the National Academy of Science, and an honorary member of the Harvey Society, and frequently has contributed articles to professional journals.

A native of Indiana, and one of 10 children of the Rev. and Mrs. George Link, Prof. Link holds three degrees from the University of Wisconsin, earning his B.S. in 1922, M.S. in 1923, and Ph.D. in 1925 in agricultural chemistry. He joined the Wisconsin faculty in 1927, becoming a full professor in 1931.