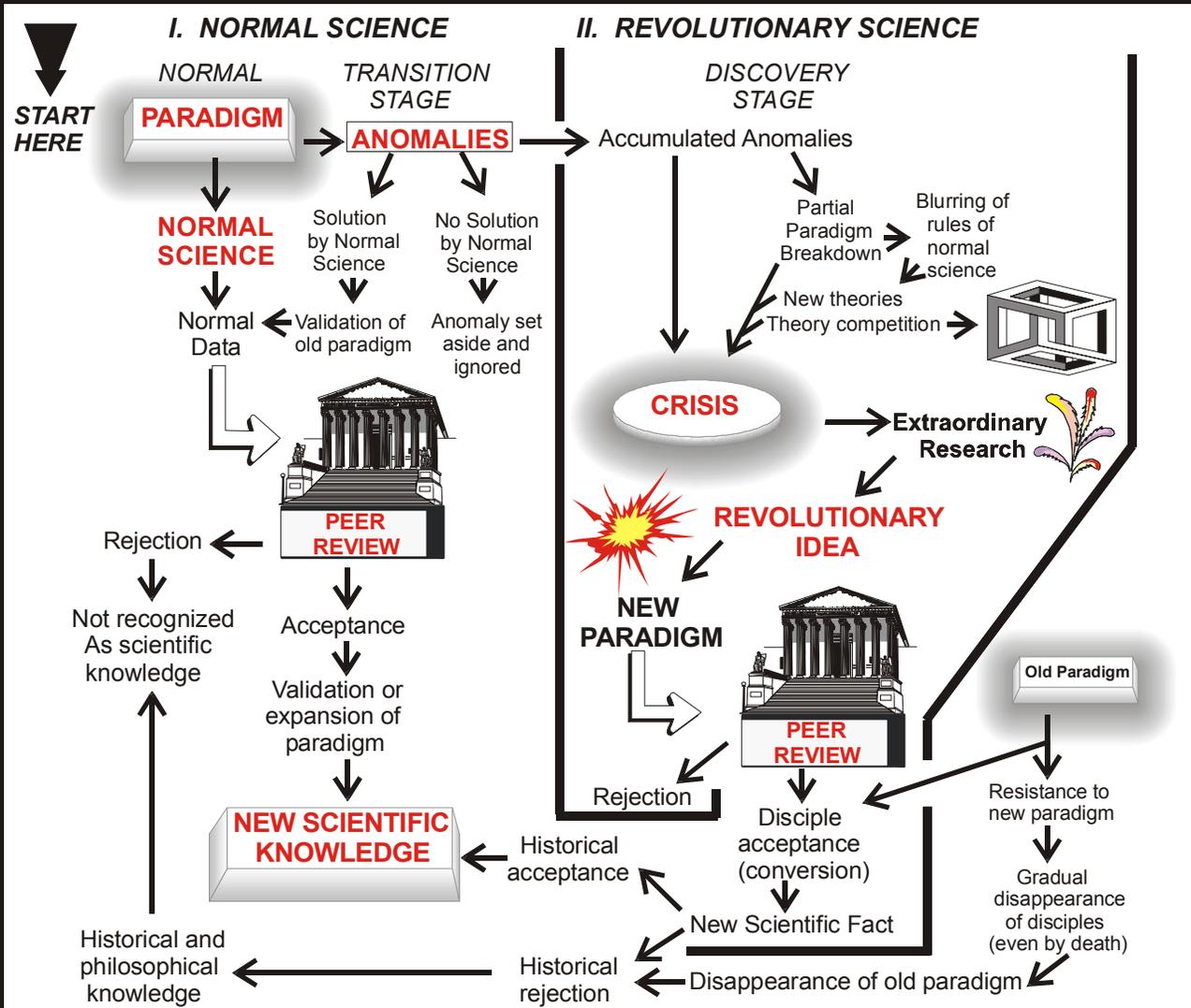
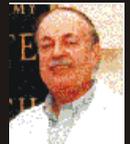


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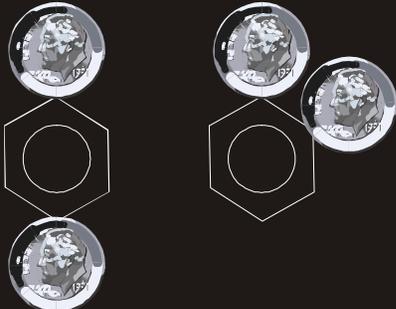
Thomas Kuhn (1922-1996)

The Structure of Scientific Revolutions (University of Chicago Press, 2nd Edition, 1970)

PARADIGMS

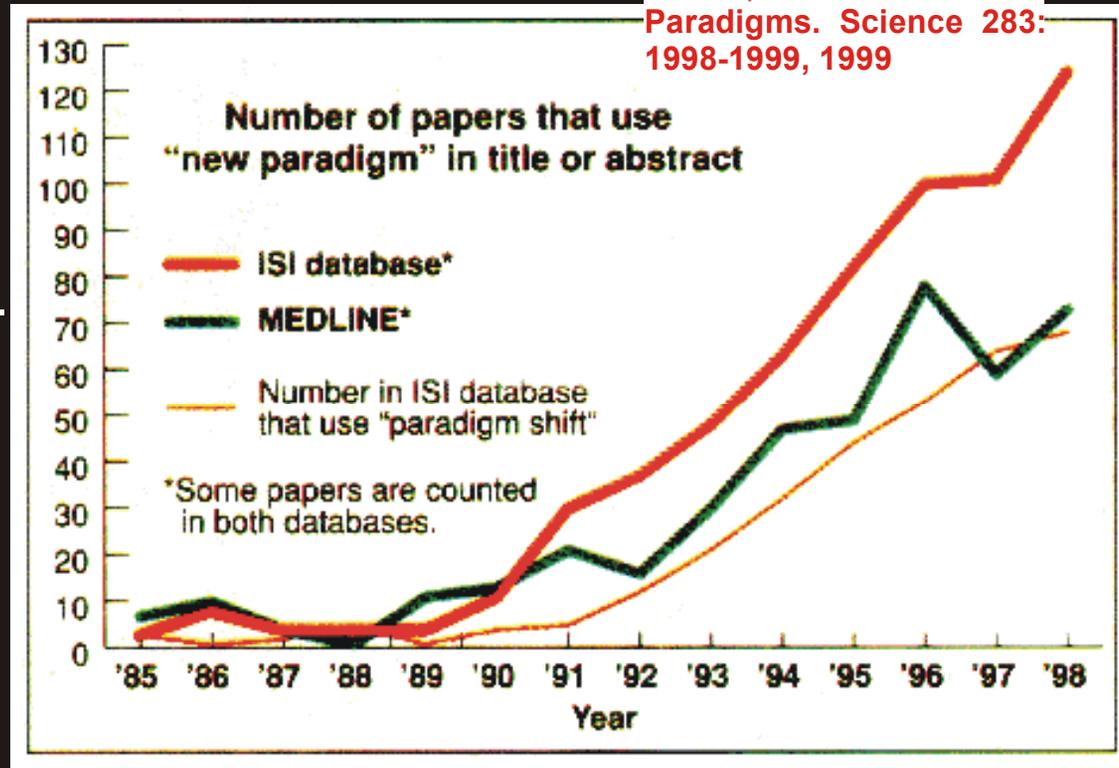


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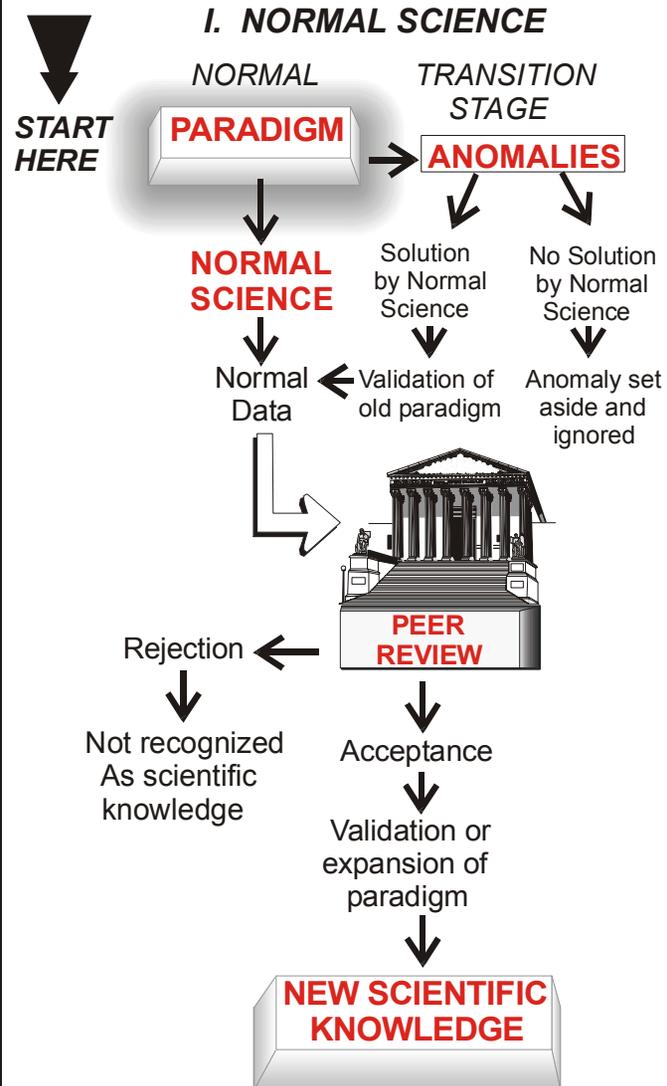
Cohen, J. The March of
Paradigms. Science 283:
1998-1999, 1999



ACCORDING TO THOMAS KUHN, AN INDEXER DISCOVERED THAT THE TERM "PARADIGM" IS USED IN AT LEAST 22 DIFFERENT WAYS IN KUHN'S BOOK, "THE STRUCTURE OF SCIENTIFIC REVOLUTIONS"

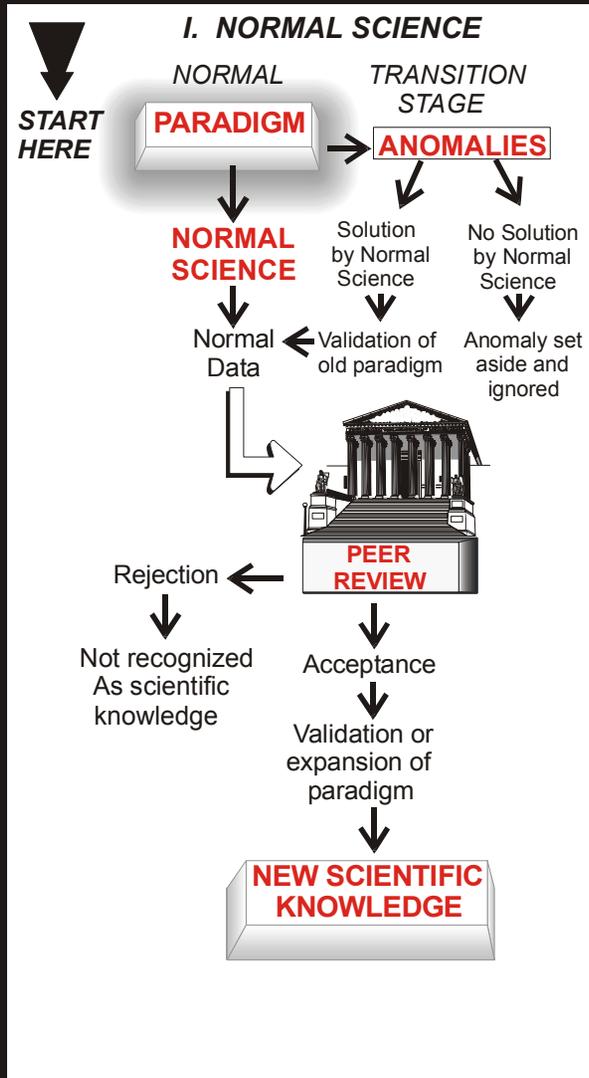
HOW SCIENCE WORKS

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PARADIGM

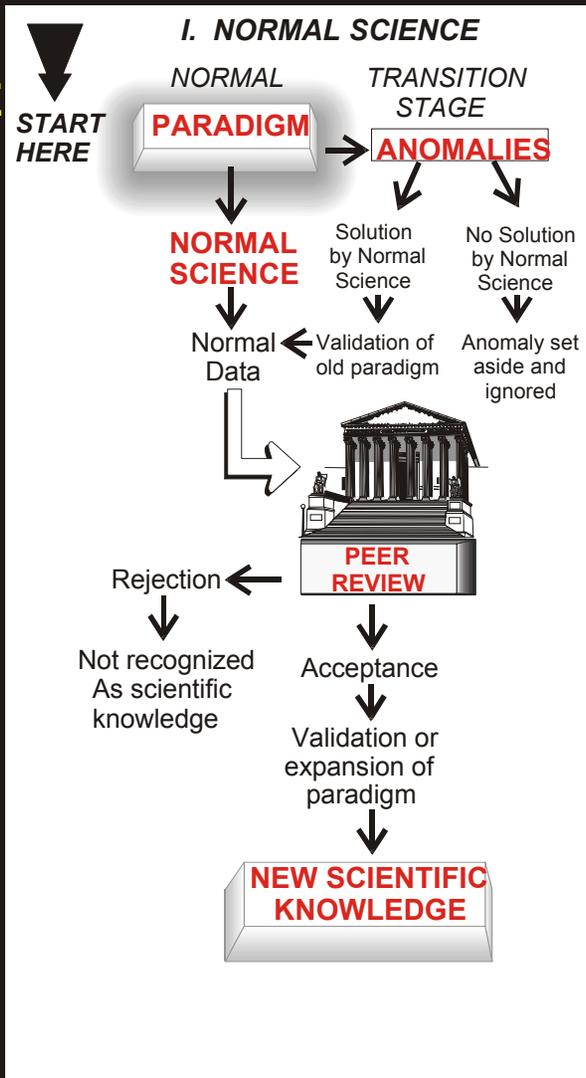
"When the individual scientist can take a paradigm for granted, he need no longer...attempt to guild his field anew, starting from first principles and justifying the use of each concept introduced." (SSR, pp. 19-20).

MESSAGE: Read the literature

"By focusing attention upon a small range of relatively esoteric problems, the paradigm forces scientists to investigate some part of nature in a detail and depth that would otherwise be unimaginable." (SSR, p. 24).

HOW SCIENCE WORKS

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NORMAL SCIENCE

"Normal science, the activity in which most scientists inevitably spend almost all of their time, is predicated on the assumption the scientific community knows what the world is like." (SSR, p. 5)

"No part of the aim of normal science is to call forth new sorts of phenomena...Nor do scientists normally aim to invent new theories and they are intolerant of those invented by others.

Instead, normal scientific research is directed to the articulation of those phenomena and theories that the paradigm already supplies." (SSR, p. 25)

MESSAGE: Do not try to make new discoveries.

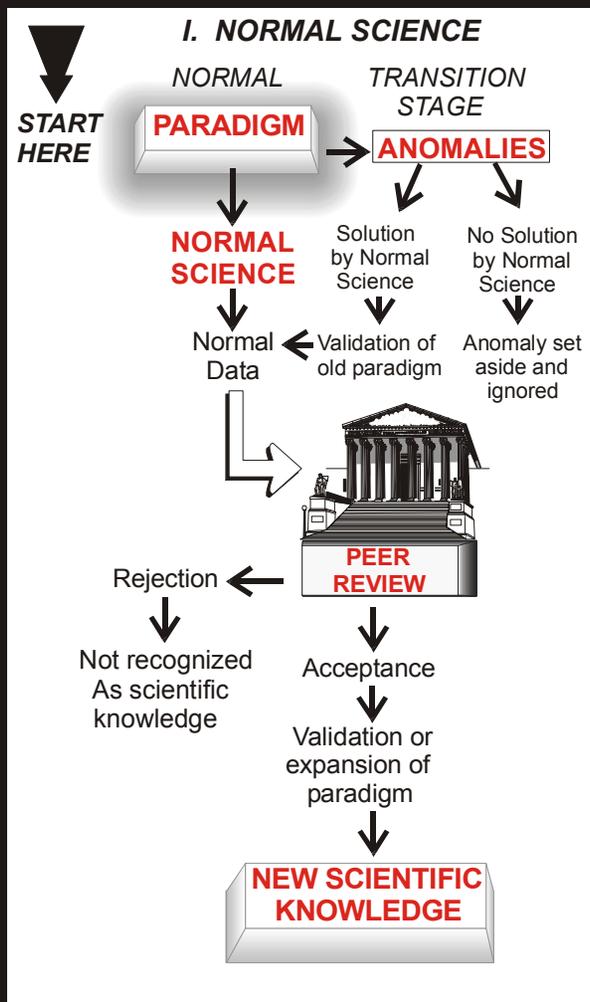
"Normal science does not aim at novelties of fact or theory and, when successful, finds none." (SSR, p. 52).

MESSAGE: New discoveries are almost always accidents

"One of the reasons why normal science seems to progress so rapidly is that its practitioners concentrate on problems that only their lack of ingenuity should keep them from solving." (SSR, p. 37)

HOW SCIENCE WORKS

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PUZZLE SOLVING

"...the unit of scientific achievement is the solved problem..." (SSR, p. 169)

"The man who succeeds proves himself an expert puzzle-solver, and the challenge of the puzzle is an important part of what usually drives him on." (SSR, p. 36).

"It is no criterion of goodness in a puzzle that its outcome be intrinsically interesting or important. On the contrary, the really pressing problems, e.g., a cure for cancer or the design of a lasting peace are often not puzzles at all, largely because they may not have any solution.

Though intrinsic value is no criterion for a puzzle, the assured existence of a solution is." (SSR, pp .36-37)

"If it is to classify as a puzzle, a problem must be characterized by more than an assured solution. There must also be rules that limit both the nature of acceptable solutions and the steps by which they are to be obtained.." (SSR, p. 38).

MESSAGE: This principle is important to embody as a set of criteria for evaluating the scientific approach when reviewing papers and grant proposals in any particular field.

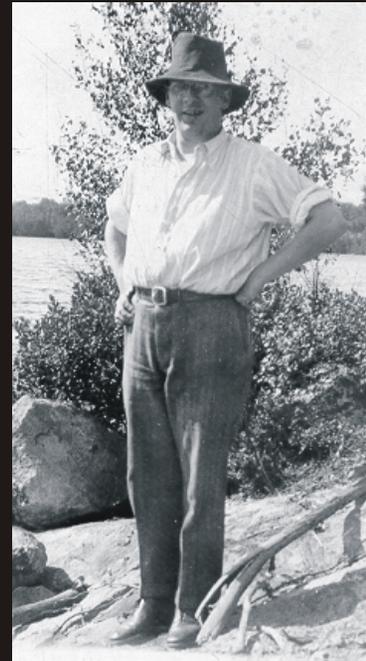
Image from the historic medical images collection of the National Library of Medicine, Bethesda, MD



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Alf Carl Dorothy

THE SIGNIFICANCE OF CONCENTRATION AND DILUTION TESTS IN BRIGHT'S DISEASE

BY ALF S. ALVING AND DONALD D. VAN SLYKE

(From the Hospital of the Rockefeller Institute for Medical Research,
New York City)

(Received for publication August 6, 1934)

The first quantitative evidence that nephritis diminishes the ability to excrete urine of either high concentration or high dilution was apparently furnished by Korányi (1899) and his collaborators, Kövesi and Roth-Schulz (1900), by means of the freezing point method. Regular application to studies of renal function, however, appears to have first begun in Volhard's (1918) clinic, where the "concentration and dilution" test has been in use since about 1908. In this test the renal function is estimated from the ability to excrete a urine of large volume and low specific gravity after drinking 1.5 liter of water (dilution test), and urine of high specific gravity after a subsequent period in which no fluid is drunk (concentration test). Modifications of these tests or their combination have been made by various authors. They have been reviewed by Pratt (1926) (with his own observations on 58 patients), by Mosenthal (1930), by Lashmet and Newburgh (1930), and with especial completeness by Volhard and Becher (1929). The simplicity of these tests, and their consequent wide application, render it desirable to define as exactly as possible the meaning of their results.

In order to obtain information for this purpose we have made graphic statistical comparisons of results of concentration tests with results of the urea clearance test, the clinical significance of which has previously been established (Van Slyke, Stillman, Möller, *et al.* (1930)¹). We have furthermore carried out prolonged observations with concentration tests and urea clearance combined on individual patients with the different types of Bright's disease, so that the prognostic significance of the tests could be deduced from the clinical outcome.

While our studies have been in progress, other data comparing results of concentration and dilution tests with results of the urea clearance test have been published by Ong (1932) from Snapper's clinic, and by Bruger and Mosenthal (1932).

¹ The terms, "standard blood urea clearance" and "maximum blood urea clearance" used in expressing the urea excreting efficiency of the kidneys, have been defined by Möller, McIntosh and Van Slyke (1928).

**J. Clin. Invest.
1934;13:969-998**

MALARIA



PROCEDURES USED AT STATEVILLE PENITENTIARY FOR THE TESTING OF POTENTIAL ANTIMALARIAL AGENTS¹

By ALF S. ALVING, BRANCH CRAIGE, JR.,² THEODORE N. PULLMAN,²
C. MERRILL WHORTON,² RALPH JONES, JR.,²
AND LILLIAN EICHELBERGER

(From the Malarial Research Unit, Department of Medicine, University of Chicago)

(Received for publication December 23, 1946)

INTRODUCTION

The need for normal human subjects to use in appraising the activity of antimalarial drugs led, in 1944, to the establishment of a clinical research unit at the Illinois State Penitentiary, Stateville, Illinois. Through an arrangement with the Department of Public Safety,³ one floor of the prison hospital and a portion of a second floor were placed at the disposal of the Malaria Research Project. Approximately 500 inmates volunteered to act as subjects.

The studies were designed primarily to yield in-

¹ This investigation was carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago. The studies were planned in cooperation with the Panel on Clinical Testing of Antimalarials of the Board for the Coordination of Malarial Studies. This work was further aided by the participation of Army Medical officers assigned to the project by the Surgeon General, U. S. Army.

Through a cooperative arrangement between Professor Clay G. Huff and Dr. Frederick Coulston, Department of Bacteriology and Parasitology, and the Malarial Research Unit, Department of Medicine, the former group bred *Anopheles quadrimaculatus* mosquitoes, supervised their infection and the inoculation of volunteers, and determined the intensity of infection in the salivary glands of the mosquitoes. The latter group assumed the responsibility for clinical care of patients studied by both groups.

The authors express their thanks to the Malaria Study Section of the National Institute of Health for editorial assistance and for arrangements in regard to the publication of this paper. They are also grateful to the Abbott Laboratories, E. I. du Pont de Nemours and Company, Inc., E. R. Squibb and Sons, Eli Lilly and Company, Sharp and Dohme, Inc., and Wyeth, Inc., for contributing toward the publication costs.

² Formerly Captain, M.C., A.U.S.

³ The authors wish to acknowledge the cooperation of the following officials in the State of Illinois who made these arrangements possible: Dwight H. Green, Governor, T. P. Sullivan, Director of Public Safety, and Joseph F. Ragen, Warden of Illinois State Penitentiary at Joliet-Stateville.

formation concerning the effect of potential antimalarial agents upon the relapse rate of sporozoite-induced *vivax* malaria. The observations also furnished information on the prophylactic and suppressive effects of the drugs tested, as well as data on their toxicology and pharmacology in man. The Chesson strain of malaria was selected for study because its short latent period between attacks (1) made feasible the rapid accumulation of information. An abundance of normal volunteers, in the younger age groups, living under standard conditions of diet and daily routine, made controlled clinical testing of antimalarial drugs possible. The institution being in a non-endemic area, accidental reinoculation was not a problem.

PROPHYLACTIC TESTS

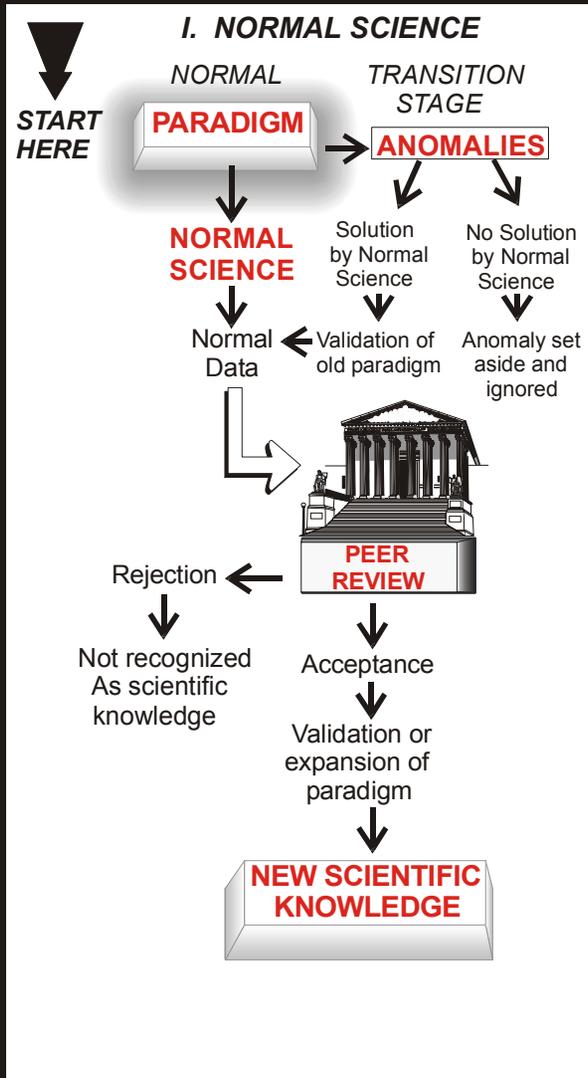
The subjects were white, male inmate volunteers in good physical health. They were acquainted beforehand with the nature of the disease and the general plan of the study. Nearly all men were in the age group of 21 to 40. Only those whose stay in the institution was ascertained to be 18 months or longer were selected. Follow-up observations could be made in nearly 100 per cent of the subjects. Volunteers who had lived in known malarious areas, or who gave a history suggestive of previous malarial infection, or who belonged to one of the colored races, were excluded in order to minimize the factors of acquired or natural immunity.

A medical history was taken and physical examinations were made on all candidates. In addition, the following procedures were routine: complete blood count, urinalysis, urinary urobilinogen concentration, phenolsulfonephthalein excretion, cephalin-cholesterol flocculation, serum bilirubin, blood nonprotein nitrogen, blood Kahn, blood typing, chest x-ray, electrocardiogram, and, where indicated, erythrocyte sedimentation rate.

J. Clin. Invest.
1948;27:2-5

HOW SCIENCE WORKS

As interpreted by Carl R. Alving, M.D. Walter Reed Army Institute of Research



WHO DETERMINES SUCCESS?

"...the members of a given scientific community provide the only audience and the only judges of that community's work." (SSR, p. 209).

MESSAGE: Publish or perish!

N.B. The above quote, as pithy and true as it may be, is the only substantive reference to *peer review* in SSR. Other than an opaque writing style for popular consumption this is the greatest flaw of the work from the perspective of a practicing scientist.

J. Clin. Invest., Vol 27(3, Pt2), 1948

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Council on Pharmacy and Chemistry

REPORT TO THE COUNCIL

The Council has authorized publication of the following report.

R. T. STORMONT, M.D., Secretary.

STATUS OF PRIMAQUINE (1-1 V)

I. MASS THERAPY OF SUBCLINICAL VIVAX MALARIA WITH PRIMAQUINE

Alf S. Alving, M.D., Chicago

Major John Arnold (MC), Army of the United States

Major Donald H. Robinson (MC), United States Army

This report deals with the problem in mass therapy presented by the large number of cases of vivax malaria occurring in the United Nations forces in Korea since 1950.

Because malaria is not a single disease but instead is a complex of diseases all caused by a member of the genus plasmodium the unique properties of the members of the various species and strains of the organism must be considered in any given therapeutic problem.

On morphologic grounds, four distinct species of plasmodia are recognized. One species, *Plasmodium ovale*, is rare and of little clinical importance; two species, *P. malariae* and *P. vivax*, have many properties in common. For therapeutic purposes, they may be considered together. The remaining species, *P. falciparum*, has special properties and must be considered separately.

On physiologic grounds, each species is made up of several strains, each with idiosyncrasies that modify response to treatment. It is unfortunate that differences in strains can usually be classified only by geography and can be considered in therapy only in the most general way. This means that drugs chosen for mass therapy must be sufficiently effective to cover variations in responses of strains.

These general considerations constitute only part of the problem faced in evaluation of antimalarial drugs.^{1a} The following discussion emphasizes those factors that are of special importance in planning a program for the eradication of malaria in troops prior to their return to the United States.

CHOICE OF TREATMENT IN RELATION TO THE TYPES OF MALARIA

P. falciparum.—*P. falciparum* appears to be the most recently acquired malaria infection in man. This is reflected in the fact that *P. falciparum* causes the greatest mortality and has the simplest life cycle of all malarias in the human host.

This simplicity of life cycle has proved to be of great importance in therapy. Very shortly after the parasite is introduced into man by a mosquito bite it disappears from the blood and enters the tissues of the host (fig. 1). Sometime within the first week of infection the tissue forms give rise to the easily recognized blood stages which usually are the only forms capable of producing symptoms. After producing this first brood of blood forms, the tissue stages either disappear or become nonfunctional. Blood forms arise only once in the course of any given infection with *P. falciparum*. For this reason, total eradication of *P. falciparum* can be achieved by simple eradication of the blood stages.

In practice, eradication of blood forms is usually easy, because most of the common antimalarial drugs have an action directed chiefly against the blood forms (schizonts). Such drugs, acting solely against the blood forms, are called suppressive agents. Of the newer suppressive drugs, chloroquine (aralen®), amodiaquine (camoquin®) and chlorguanide (paludrine®) have

Report of the Army Malaria Mission to the Far East Command during the Summer of 1951.

1a. Shannon, J. A.: Evaluation of Antimalarial Drugs, chap. 10 in Evaluation of Chemotherapeutic Agents, C. M. MacLeod ed., New York, Columbia University Press, 1949, pp. 134-151. Singh, J.: Antimalarial Drugs, *Indian J. Malariology* 4: 185-188 (June) 1950.

largely displaced quinacrine (atabrine®) and quinine in military use.

P. Vivax.—In contrast to *P. falciparum*, infections with *P. vivax* are much better adapted to the human host. This improved adaptation of parasite to host has led to a lower mortality rate but a higher degree of persistence, which has been achieved by the development of another stage in the life cycle of the parasite. *P. vivax* begins, like *P. falciparum*, as a tissue infection which lasts approximately one week, at the end of which time the blood forms causing the primary attack are produced (fig. 2). From this point on an important difference between *P. falciparum* and *P. vivax* appears. In the latter infection, a persisting tissue stage develops which, by giving off broods of blood forms at intervals, accounts for the periodic relapses of vivax malaria.

All the suppressive drugs effective against the blood forms of *P. falciparum* are effective against the blood forms of *P. vivax*. Thus, drug therapy of the acute disease from either parasite is usually the same, but the long-term result of such therapy is quite different. In *P. falciparum* infections, adequate suppressive therapy eliminates the disease for all time; in *P. vivax* infections, suppressive therapy eliminates symptoms of the disease until the next relapse.

If suppressive agents are taken continuously and in sufficient amounts, the blood forms produced in *P. vivax* infections at intervals by the persisting tissue stages are destroyed soon after they are formed and the patient remains well. Because vivax malaria is a self-limiting disease, through the development of immunity or the exhaustion of the tissue stages, continuation of suppressive medication for several years after leaving a malarious area will result in a reduction of the relapse rate. In endemic areas, continuous suppression can be carried out successfully for years provided a break in drug administration does not occur. Such long-continued suppression requires continuous vigilance. This is difficult even in endemic areas but is usually impossible for individuals or organizations returning to nonendemic areas where the stimulus for continuous therapy is lacking.

RADICAL CURE OF VIVAX MALARIA

To meet the problem produced by the constant threat of relapse from vivax infections in persons leaving an endemic area for a nonendemic area, another class of antimalarial drugs is of value. This class of drugs acts by destroying the tissue stages of the disease and thereby prevents the development of the blood form responsible for the relapse. Since they completely eliminate all trace of the infection, these drugs are called curative as opposed to the suppressive drugs which destroy only blood forms. Unfortunately, the curative drugs now known have very little effect against the blood forms and must be used in conjunction with one of the suppressive drugs when blood forms of the disease are present.

Of the thousands of drugs studied for antimalarial action, only members of the 8-aminoquinoline family closely related to primaquine have shown a significant amount of curative activity. A number of compounds of this family possess some degree of action against the tissue stages of malaria, but only one of these compounds has shown a high enough level of activity with a low enough level of toxicity to warrant its use on a large scale. This compound, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, now known as primaquine, was synthesized at Columbia University during the World War II antimalarial program.¹ After the wartime program was terminated, primaquine received extensive animal studies at The Christ Hospital, Cincinnati,² clinical tests at Stateville Penitentiary and the Federal Penitentiary at Atlanta,³ and actual field trials in Nicaragua.⁴ Large scale toxicity studies

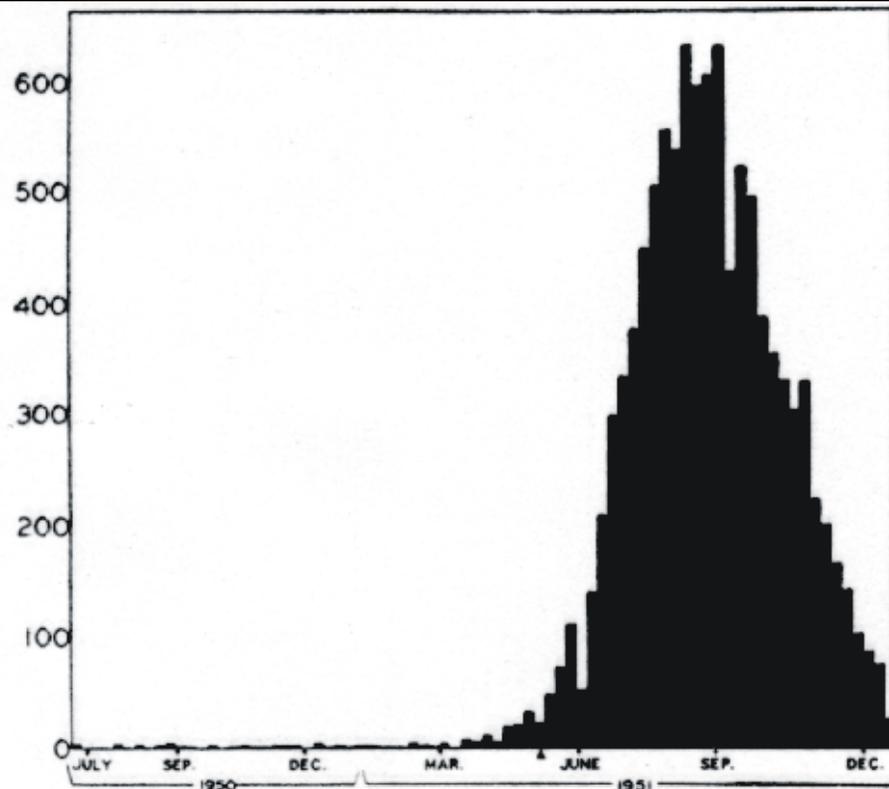
1. Elderfield, R. C., and others: Alkylaminoalkyl Derivatives of 8-Aminoquinoline, *J. Am. Chem. Soc.* 68: 1524-1529 (Aug.) 1946.

2. Schmidt, L. H.: Unpublished data.

3. Edgcomb, J. H., and others: Primaquine, S. N. 13,272, A New Curative Agent in Vivax Malaria: A Preliminary Report, *J. Nat. Malaria Soc.* 9: 285-292 (Dec.) 1950. Clayman, C. B.; Arnold, J.; Hockwald, R. S.; Yount, E. H., Jr.; Edgcomb, J. H., and Alving, A. S.: Toxicity of Primaquine in Caucasians, *J. A. M. A.*, this issue, p. 1563. Coatsney, R. G., and others: Unpublished data on clinical studies of primaquine conducted at Atlanta Penitentiary.

4. Traeger, A. D., Jr.; Arnold, J., and Alving, A. S.: Field Studies of Primaquine in Nicaragua, presented at the Annual Meetings of the National Malaria Society, Chicago, Nov. 14-17, 1951.

J. Am. Med. Assn.
1952;149-1558-1562



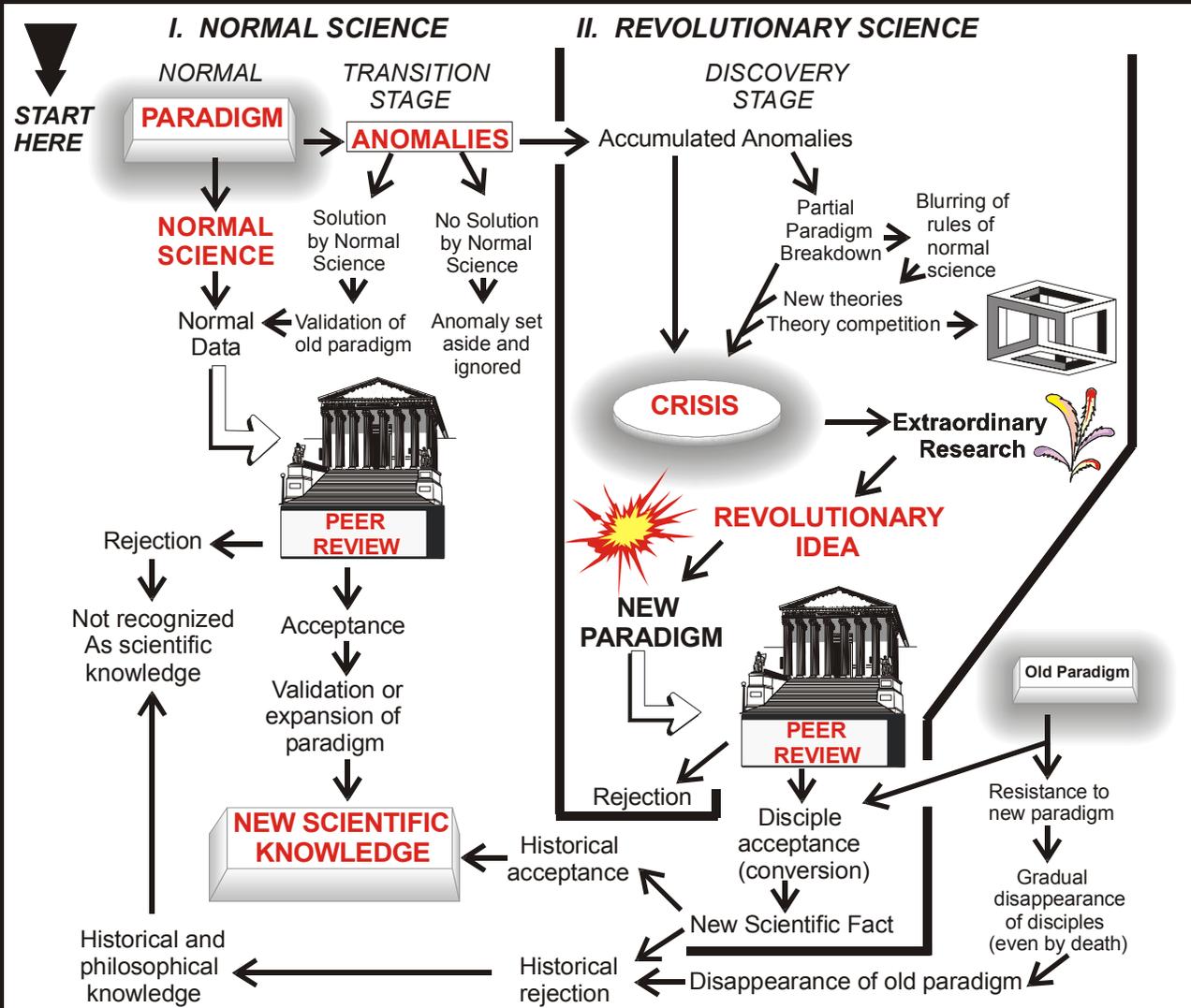
▲ FIRST SHIP LOAD KOREA VETERANS LANDED IN U. S. MAY 5, 1951

Fig. 4.—Number of Army personnel hospitalized for malaria in the United States each week since onset of Korean conflict. (Source: Medical Statistics Division, Office of the Surgeon General, Department of the Army.)

**J. Am. Med. Association
1952;149:1558-1562**

HOW SCIENCE WORKS

As interpreted by Carl R. Alving, M.D. Walter Reed Army Institute of Research



Thomas Kuhn (1922-1996)

The Structure of Scientific Revolutions (University of Chicago Press, 2nd Edition, 1970)

Although mild decrease in hemoglobin occasionally has occurred at both high and low doses, severe hemolytic anemia has not been encountered during this study involving 699 white adults receiving primaquine in dosages as high as 240 mg. daily. Severe hemolytic anemia, however, has been observed in Negroes after dosages as low as 30 mg.¹⁶ Because of the potential hemolytic activity of the drug, primaquine should not be administered to persons having complicating diseases characterized by a hemolytic tendency.

Primaquine, at 15 mg. daily, can be administered safely for two weeks without special medical supervision. At 30 mg. daily, primaquine may occasionally produce minor symptoms but can be safely administered to white patients under observation on an out-patient basis. At higher dosage schedules, hospitalization is desirable.

Quinacrine (atabrine[®]) potentiates the toxicity of pamaquine¹⁷ and pentaquine.¹⁸ Until the effect of quinacrine on primaquine toxicity has been determined, it would seem inadvisable to institute primaquine treatment until several weeks have elapsed following termination of treatment with this suppressive agent. Suppressant agents, at present, should be restricted to quinine and chloroquine, of which the latter is the drug of choice.

A comparison of primaquine and pamaquine can be complete only if the toxicity of the two drugs is correlated with their relative curative action on an equal weight basis; in this respect primaquine is at least four times as effective.

CONCLUSIONS

Primaquine has been administered to 699 adult white subjects in a dosage range of 10 to 240 mg. per day. On the basis of symptoms and laboratory findings it is concluded that, at dosages of 15 mg., primaquine may be safely administered daily for two weeks without special medical supervision. Adult white patients may be followed on an ambulatory basis when receiving doses as high as 30 mg. per day. If it is ever used at higher dosages or administered to patients having diseases known to affect the bone marrow or blood, primaquine should be given only during hospital supervision.

Weekly and semiweekly administration of primaquine for as long as 52 weeks in doses of 30 mg. to 50 subjects did not reveal dangerous toxicity when combined with 0.3 gm. of chloroquine. (All dosages have been expressed in terms of base weight.)

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4. TOXICITY OF PRIMAQUINE IN NEGROES

Capt. Robert S. Hockwald, Major John Arnold, and Capt. Charles B. Clayman, (MC), United States Army Alf S. Alving, M.D., Chicago

Hemolytic reactions during antimalarial therapy have proved to be a limiting factor in the use of 8-aminoquinolines for the cure of vivax malaria. The most severe type of reaction is clinically identical to blackwater fever, and is characterized by massive, explosive, intravascular hemolysis with hemoglobinemia and hemoglobinuria, which constitutes a medical emergency necessitating immediate transfusions. Acute hemolysis has been observed during the therapeutic use of a number of 8-aminoquinolines, for example, pamaquine,¹ pentaquine,² and isopentaquine.³ The incidence of hemolytic reactions is higher in the dark-skinned races. According to Earle and co-workers,⁴ 5 to 10% of Negroes contract acute hemolysis when given 30 mg. or more of pamaquine daily. Only 1% of white subjects studied by him contracted hemolysis which, however, was not acute.

PROCEDURES

Dosage Schedules.—Primaquine 18-(4-amino-1-methylbutylamino)-6-methoxy quinoline, 30 mg. of base daily, was administered orally in single or divided doses to 110 normal male

Negro volunteers at Stateville Penitentiary. The men ranged in weight from 130 to 240 lb.; the average being 165 lb. Primaquine was given, alone or concurrently with quinine or chloroquine, for 14 days. This dose is slightly larger than that usually recommended for therapy.

The following four schedules were used:

1. Fifty men were given 30 mg. of primaquine base in a single daily dose for 14 days.
2. Twenty-five men were given 30 mg. of primaquine base daily concurrently with 2 gm. of quinine sulfate (1.64 gm. of base) daily for 14 days (both drugs were administered in six divided doses).
3. Twenty-five men were given 30 mg. of primaquine base in a single daily dose for 14 days concurrently with single doses of chloroquine base, 0.6 gm. on the first day and 0.45 gm. on the second day.
4. Ten men were given 30 mg. of primaquine base for 14 days concurrently with chloroquine base, 0.6 gm. on the first day, 0.45 gm. on the second day, and 0.3 gm. on each of the next 12 days. Both drugs were administered in single daily doses.

The men contracting severe anemia while receiving the 30 mg. dosage subsequently were given 15 mg. of primaquine base orally once daily for 14 days to determine whether the reduced dosage would also produce hemolysis.

Later, the same subjects were given pamaquine orally, 30 mg. of base once daily, to compare the hemolysis with that produced by 30 mg. of primaquine base.

Primaquine, 15 mg. of base, was administered orally, once daily, for 14 days to a second group of 50 normal male Negro volunteers. These men ranged in weight from 127 to 211 lb., the average being 161 lb. The primaquine was given alone or concurrently with chloroquine, 0.6 gm. of base on the first day and 0.45 gm. on the second day. This dose of primaquine has been adopted for routine interim treatment of malaria in Korean veterans.⁵

Special Observations and Laboratory Studies.—Each man was questioned daily to detect unusual symptoms. Methemoglobin and hemoglobin levels were determined daily, three and seven days after drug administration was completed. A white blood cell count was taken initially, every two days while the drug was being given, and three and seven days afterward. Differential white counts were performed initially and thereafter if any significant change in the total white count occurred. A urinalysis was performed before the drug was given, and was later repeated if a marked drop in hemoglobin occurred. The following liver function tests were performed on 32 of the men receiving the 30 mg. dosage: total plasma proteins,⁶ 30-minute bromsulphalein retention test,⁷ serum bilirubin (direct and indirect),⁸ thymol turbidity,⁹ Red blood cells from men who developed severe anemia were tested for osmotic fragility and sickling.¹⁰

Severity of hemolytic reactions was evaluated in the following manner:

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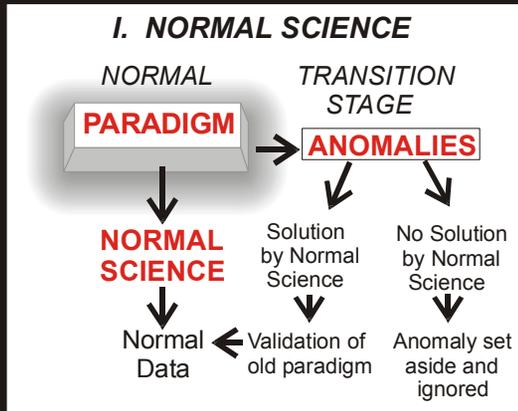
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HOW SCIENCE WORKS

As interpreted by Carl R. Alving, M.D. Walter Reed Army Institute of Research



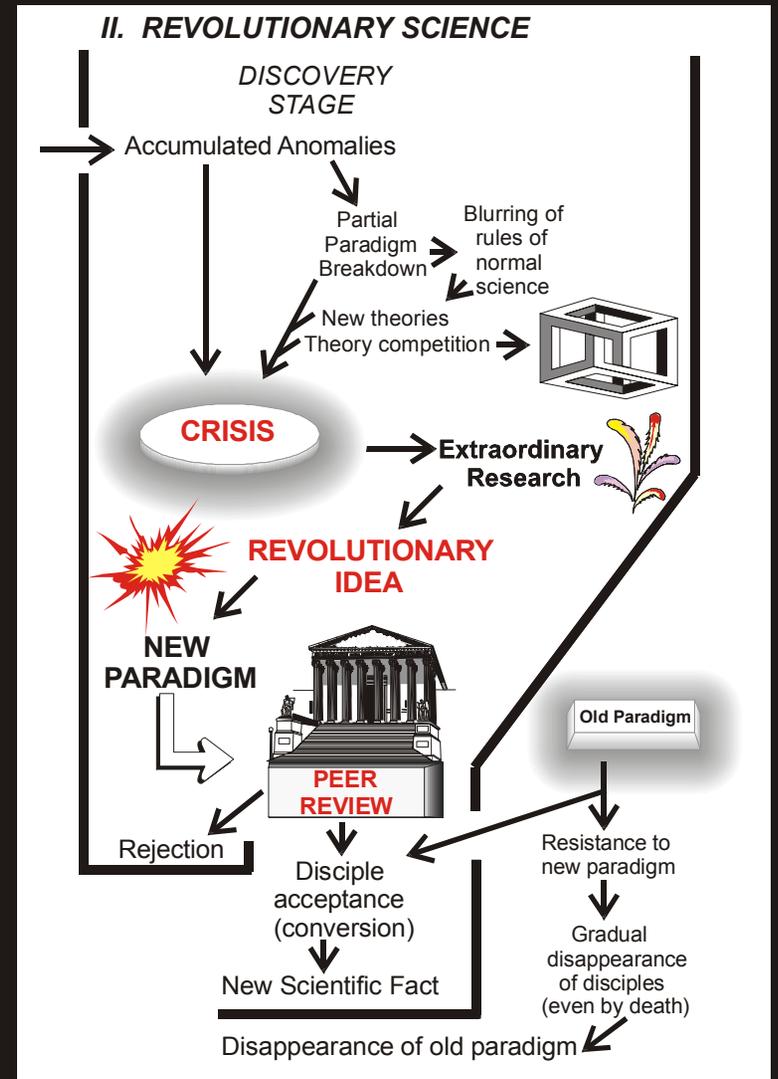
ANOMALY

"Novelty ordinarily emerges only for the man who, knowing with precision, what he should expect, is able to recognize that something has gone wrong. Anomaly appears only against the background provided by the paradigm."
(SSR p. 64)

"Discovery commences with the awareness of anomaly, i.e., with the recognition that nature has somehow violated the paradigm-induced expectations that govern normal science."

"It then continues with a more or less extended exploration of the area of anomaly."

"And it closes only when the paradigm theory has been adjusted so that the anomalous has become the expected."
(SSR, pp 52-53)



Mitigation of the Haemolytic Effect of Primaquine and Enhancement of its Action against Exoerythrocytic Forms of the Chesson Strain of *Plasmodium vivax* by Intermittent Regimens of Drug Administration*

A Preliminary Report

ALF S. ALVING, M.D.,¹ CHARLES F. JOHNSON, ALVIN R. TARLOV, M. D.²
GEORGE J. BREWER, M.D.,³ ROBERT W. KELLERMAYER, M.D.,⁴ & PAUL E. CARSON, M.D.⁵

Primaquine—an 8-aminoquinoline derivative—is one of the most effective drugs for use against the tissue stages of the malaria parasite. Unfortunately certain persons suffer from an inherited defect of metabolism which renders them susceptible to haemolysis after ingestion of the 8-aminoquinolines, certain other drugs and some vegetables. Susceptibility appears to be inherited by a partially dominant sex-linked gene of variable expression. In persons with full expression of this defect, intravascular haemolysis may be of such severity as to mimic blackwater fever.

It has been shown that the haemolysis caused by daily doses of primaquine is self-limited, provided that such doses are not excessive, by virtue of the fact that the younger erythrocytes are relatively resistant to destruction by the drug.

Therapeutic studies reported in the present paper indicate that the toxicity is markedly diminished by regimens requiring administration in weekly doses (together with the standard suppressive dose of chloroquine or one of its congeners) while its therapeutic effectiveness in the radical cure of Chesson vivax malaria is increased.

A weekly dose of 45 mg primaquine proved highly effective against severe Chesson vivax infections when administered for eight weeks. It cured 90% of infections, yet did not produce clinically demonstrable haemolysis in primaquine-sensitive adult males with major expression of the haemolytic trait.

INTRODUCTION

Since 1945 Alving and his associates have conducted intensive investigations of the toxicity of newly synthesized 8-aminoquinolines, and of their causal prophylactic and curative (anti-relapse) activity in severe, mosquito-induced Chesson vivax

malarial infections of inmate volunteers at the University of Chicago—Army Medical Research Unit in the Illinois State (Stateville) Penitentiary. The Chesson south-west Pacific strain, most likely of New Guinea origin, has been used in the therapeutic trials because it presents a very severe, possibly the most severe, challenge to radical cure by 8-

* From the University of Chicago—Army Malaria Research Unit. The investigations have been supported in major part by the Research and Development Command, Office of the Surgeon General, Department of the Army, under contract with the Department of Medicine, University of Chicago (current contract No. DA-49-007-MD-566).

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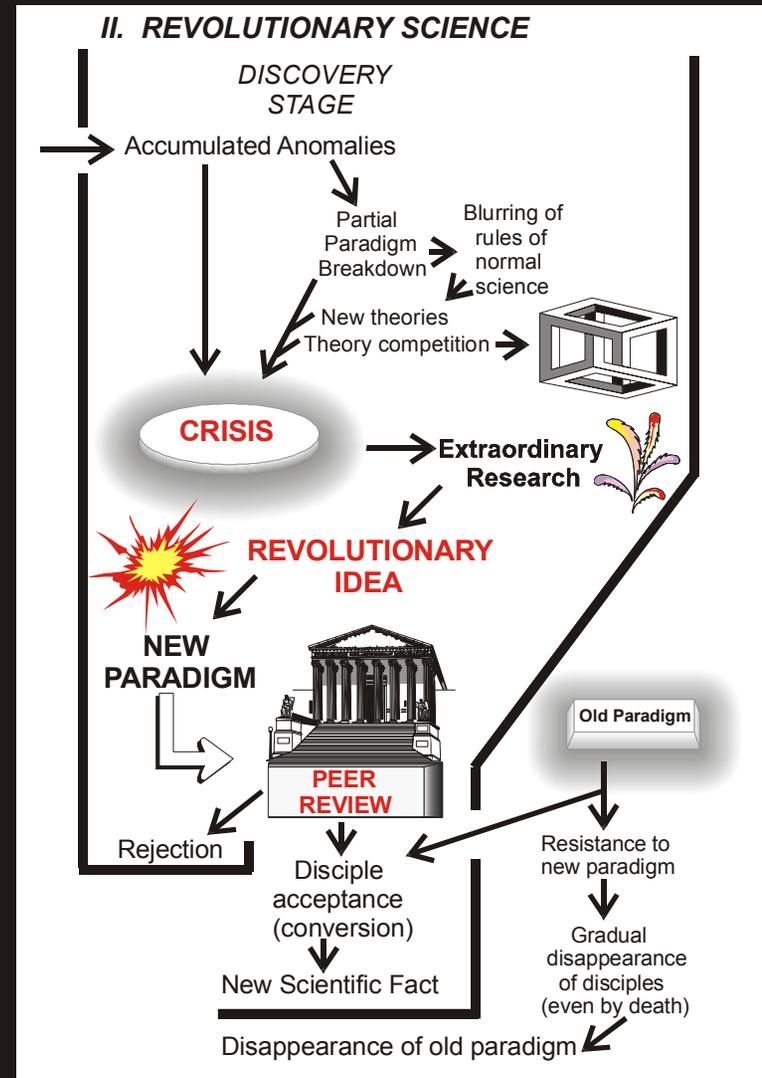
**Bull. Wld. Hlth. Org.
1960;22:621-631**

HOW SCIENCE WORKS

As interpreted by Carl R. Alving, M.D. Walter Reed Army Institute of Research

CRISIS

"Because it demands large-scale paradigm destruction and major shifts in the problems and techniques of normal science, the emergence of new theories is generally preceded by a period of pronounced professional insecurity." (SSR pp. 67-68)



HOW SCIENCE WORKS

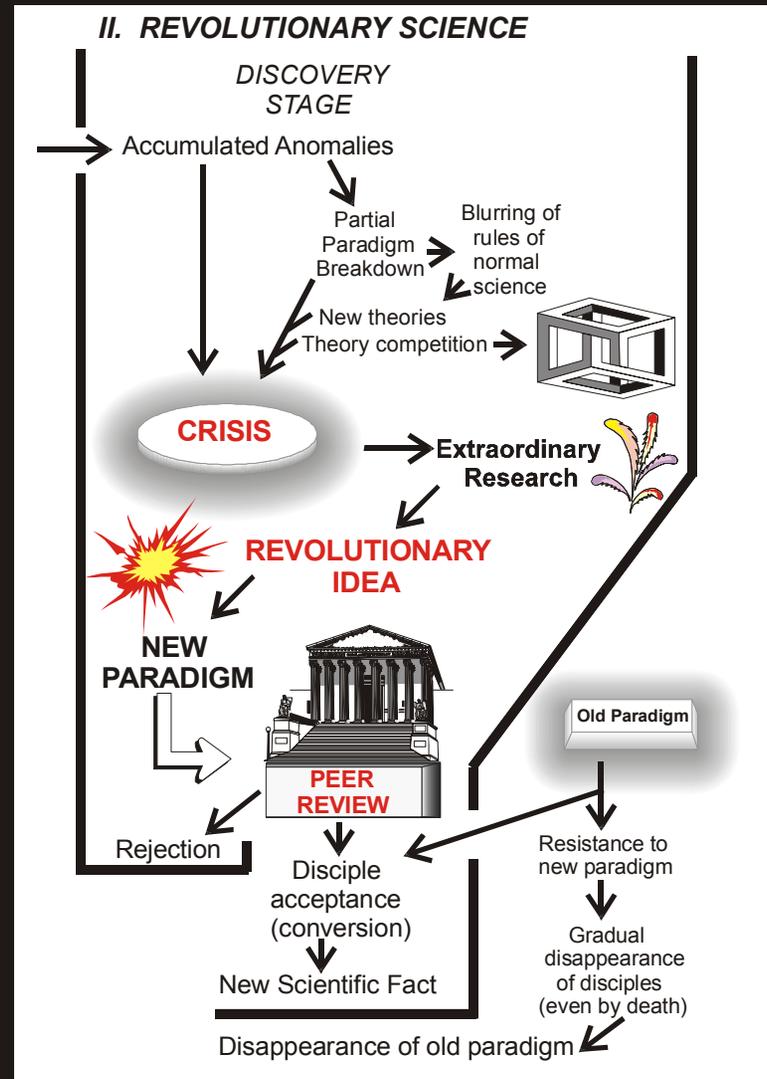
As interpreted by Carl R. Alving, M.D. Walter Reed Army Institute of Research

SUCCESSFUL NEW PARADIGM

"First, the new candidate must seem to resolve some outstanding and generally recognized problem that can be met in no other way.

Second, it must promise to preserve a relatively large part of the concrete problem-solving ability that has accrued through its predecessors.

Novelty for its own sake is not a desideratum in the sciences as it is in so many other creative fields." (SSR, p 169)



SCIENCE 124:484-485
(1956)
Reports

Space-Time Relationships in Somesthetic Localization

It has been suggested recently that the representation of somesthetic space depends on temporal patterns of neuronal discharge in the parietal association areas of the cerebral cortex (1). This suggestion was based on the discovery that there are neurons in these areas which may be aroused from any of several points on the periphery, but with different latencies. It is likely therefore, that time and space should be interchangeable to some degree, and that increasing the temporal separation of two stimuli should decrease the spatial separation necessary for them to be judged as in different places. Such is actually the case for touch. It is well known that the two-point threshold (stimuli simultaneously presented) is considerably greater than the error of localization (stimuli successively presented) (2). But the temporal relationships have not been studied in detail, as is necessary if the neurophysiological and psychophysical data are to be correlated. The experiment reported here is a step in that direction (3).

The minimum separation of two stimuli to the skin which led them to be judged to be in different places was determined for each of several temporal intervals between them. The stimuli, electric square waves of 0.5-msec duration, were presented to the forearms of two subjects through silver-silver chloride wick electrodes. The stimuli were generated by a "two-shot" stimulator built in the department of physiology and biophysics, University of Washington. Intervals, from the end of pulse one to the be-

Table 1. Minimum separation, in centimeters, judged as "different place" by subjects F.N.J. and M.H.J.

Interval (msec)	F.N.J.		M.H.J.	
	Mean	S.D.	Mean	S.D.
2.1	11.0	1.4	11.8	1.2
3.0	10.6	.5	10.3	1.4
12.0	10.2	1.0	10.9	1.0
102.0	7.1	1.4	7.7	2.8
1001.0	4.5	.8	3.0	.9

ginning of pulse two, of 0.1, 1.0, 10.0, 100.0, and 1000.0 msec were used. Since the more distal of the two stimuli was always the second pulse, these intervals are about 2.1, 3.0, 12.0, 102.0, and 1001.0 msec when allowance is made for the extra conduction time. Four determinations of spatial separation were made for each interval on each subject at a single sitting, using the "up and down" method (4). Each subject had four sittings, with the different intervals given in balanced order, so that each threshold is based on 16 measurements. Considerable care was used to insure pure pressure stimulation, painful spots being discarded, and the intensity of stimulation was adjusted each time an electrode was moved to maintain a moderately strong pressure sensation. Subjects' reports consisted either of "same place" or "different place," because at the longest intervals the duality of stimulation was evident. Apparent movement was sometimes observed but did not interfere with the judgments.

The data are given in Table 1. If the shortest interval is taken to represent the two-point threshold and the longest is taken to approximate the error of localization, the data are in agreement with the older research. There is significant interaction of space and time, and increasing the interval reduces the separation necessary to produce the report of "different place."

The question now arises whether the psychophysical and neurophysiological data are consistent. If allowances are made for species differences and for the effects of anesthetics, the answer is in the affirmative. Amassian's "blocking" effects for the AAP (association-area positive response) extend over as many as 600 msec and are consistently noted below 150 msec. In the experiment reported here, the region of most rapid change in spatial threshold lay between 10 and 1000 msec, with only a slight change, if any, between 2 to 10 msec. The error of localization is approximated at about the interval necessary for blocking to be ineffective. The blocking could account for the lack of fine discrimination because the necessary information does not reach the parietal association areas.

There are possible alternative explana-

tions of the psychophysical data. Some years ago Boring suggested that the difference between the two-point threshold and the error of localization could be due to the spread of excitation in the brain (he had mechanical stimulation in mind) (5). He did not have precise temporal data available, and the present data because of the relatively large critical intervals, do not favor a peripheral explanation. The same spread-of-excitation argument could be extended to the relay nuclei and the primary sensory cortex, however. Isomorphic theories of space perception have been popular, and if two-point tactual discrimination is considered to be based on two regions of excitation in the primary cortex, it may also be that temporal separation permits better differentiation of these regions. This would imply that the "sharpening" process imputed to some sensory systems is proved by the delay of one afferent process, an implication that is not borne out by experimentation on vision (6). When it is considered in addition that lesions in the parietal association areas may lead to a severe deficit in somesthetic perception (7), the suggestion that space perception in the pressure sense arises from the translation of spatial patterns in the primary sensory cortex into temporal patterns in the association areas has less plausibility and appeal. If this suggestion should prove correct, it will be of considerable aid in clarifying the problem of the neurophysiological basis of perception.

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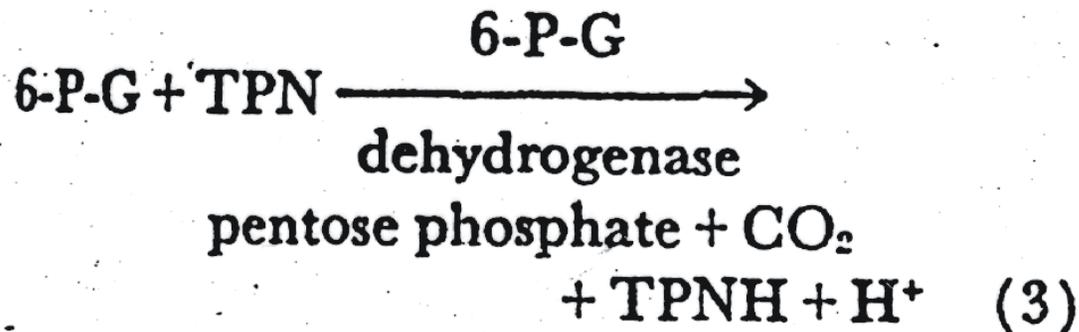
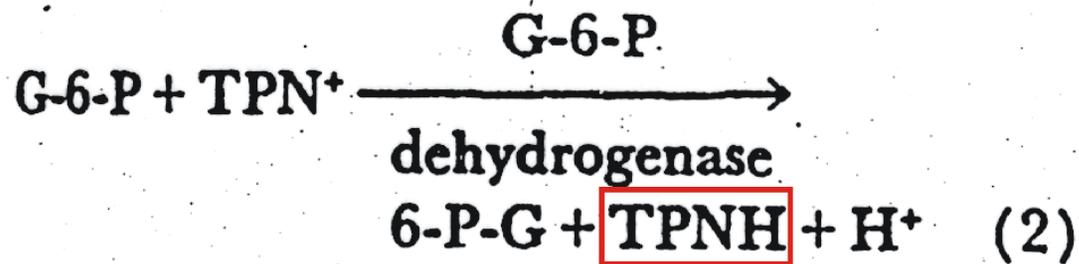
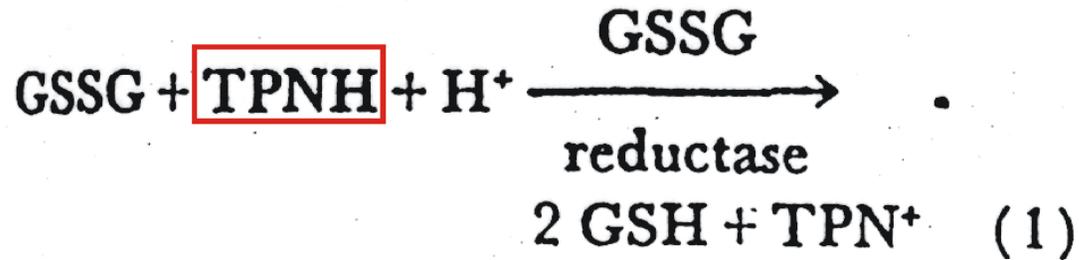
References and Notes

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- 2 July 1956

Enzymatic Deficiency in Primaquine-Sensitive Erythrocytes

Primaquine, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, induces intravascular hemolysis in about 10 percent of Negroes, but rarely in Caucasians (1). This hemolysis is due to a defect of the red blood cells (2).

Science
1956;124:484-485



HOW SCIENCE WORKS

As interpreted by Carl R. Alving, M.D. Walter Reed Army Institute of Research

PEER REVIEW AND PARADIGM CHOICE

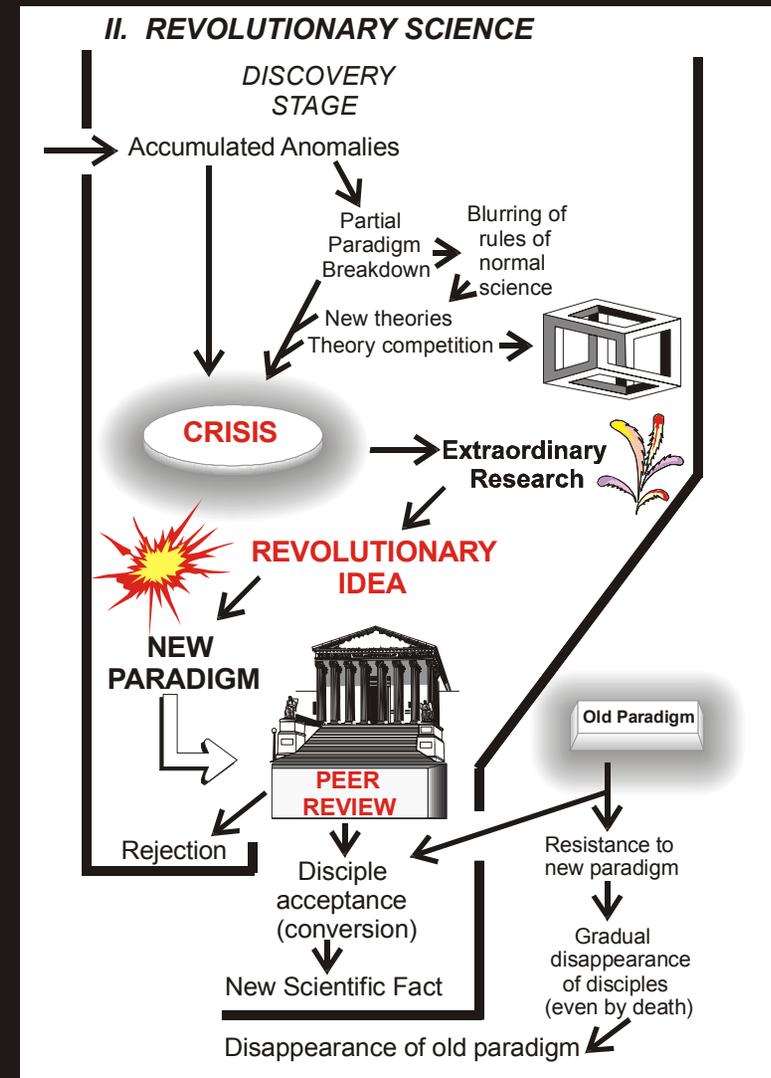
"As in political revolutions, so in paradigm choice---there is no standard higher than the assent of the relevant community.

Scientific revolutions are effected...not only by the impact of nature and logic, but also by the techniques of persuasive argumentation effective within the quite special groups that constitute the community of scientists." (SSR, p. 94)

MESSAGE: Publish or perish (even as a government scientist)

RESISTANCE TO NEW PARADIGM

"By ensuring that the paradigm will not be too easily surrendered, resistance guarantees that scientists will not be lightly distracted and that the anomalies that lead to paradigm change will penetrate existing knowledge to the core." (SSR p. 65).



HOW SCIENCE WORKS

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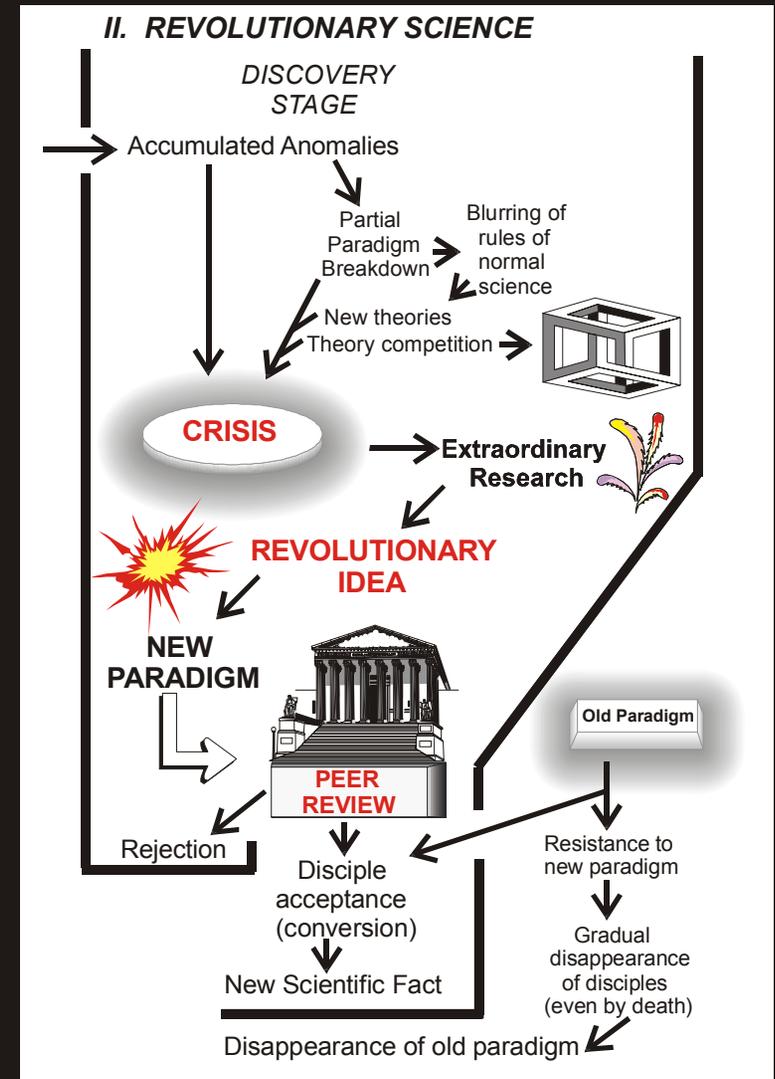
DISAPPEARANCE OF OLD PARADIGM

"...the man who continues to resist after his whole profession has been converted has *ipso facto* ceased to be a scientist." (SSR, p. 159).

MESSAGE: You can't convince everyone

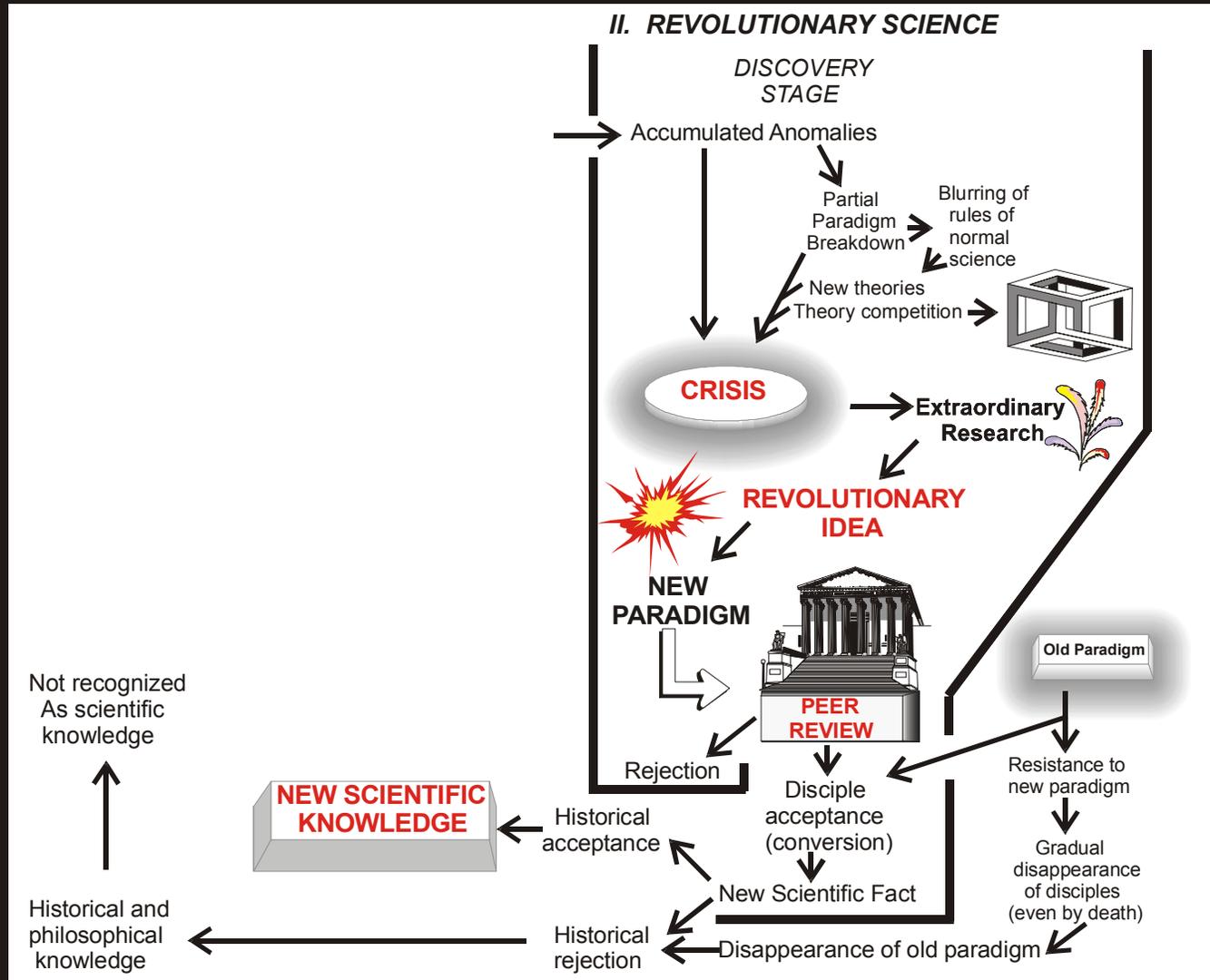
...Max Planck, surveying his own career, sadly remarked that "a new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die" (SSR, p. 151))

MESSAGE: You can't convince everyone

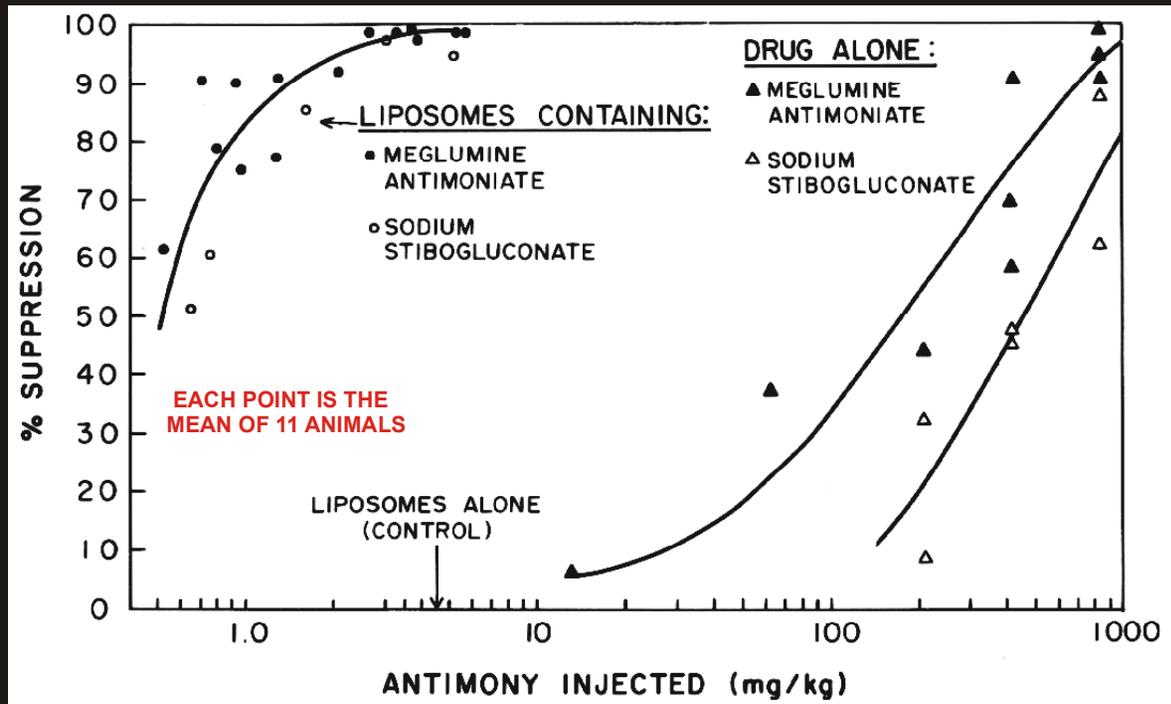


HOW SCIENCE WORKS

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LIPOSOMES AS DRUG CARRIERS TO TREAT EXPERIMENTAL LEISHMANIASIS IN HAMSTERS



CONCLUSION:

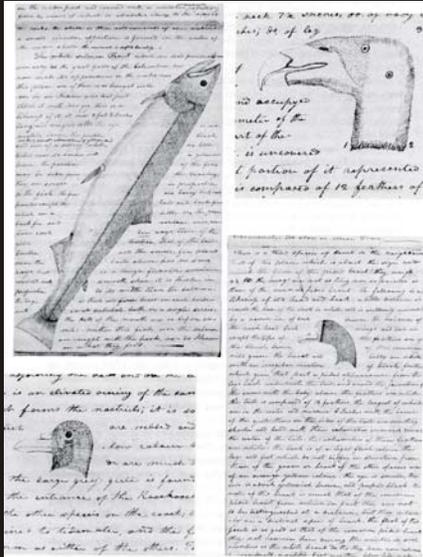
LIPOSOMES CONTAINING ANTIMONIAL DRUGS ARE MORE THAN 700-FOLD MORE EFFECTIVE THAN THE DRUGS ALONE IN THE TREATMENT OF EXPERIMENTAL LEISHMANIASIS

Alving et al., Proc. Natl. Acad. Sci. USA 75:2959-2963, 1978

For review, see Alving, C. R. Parasitology Today 2:101-107, 1986

From: "Undaunted Courage. Meriwether Lewis Thomas Jefferson and the Opening of the American West", by Stephen Ambrose, Simon & Schuster, NY 1996 (paperback edition)

The publication history of the U.S. Army Scientific expedition ("Corps of Discovery") led by Captains Lewis and Clark to explore and describe the territory of the Louisiana Purchase.



Lewis's sketch of, clockwise, a trout, a vulture, a brant, and a gull, in his journal. (Courtesy American Philosophical Society)

- "The enlightenment taught us that observation unrecorded was knowledge lost." (P. 421)
- "Sitting around the campfire, cold, hungry, exhausted, and miserable, Lewis summoned the energy to make significant additions to scientific knowledge (if he could get his journals back to civilization)" (P. 295)
- "Lewis was blessed with abilities often missing in naturalists, particularly an outstanding, inherent observational competence, an all-inclusive interest, and an objective, systemic, philosophical approach to understanding the natural world. Nothing refutes Lewis's self-appraisal [as a botanist], and deprecating remarks of others, more elegantly than his own abundant writing ...In the context of the day, Lewis was an unusually capable naturalist, one with an attitude more consistent with scientists of the twentieth century than with those of his own." (P. 331)
- Because of an inexplicable prolonged delay by Lewis in arranging publication of the journals, several years elapsed until 1914 when a paraphrase of the journals was published under the editorship of Biddle after the death of Lewis. "For the next ninety years, Biddle's edition was the only printed account based on the journals. As a result, Lewis and Clark got no credit for most of their discoveries. Plants, animals, rivers, birds that they had described and named were newly discovered by naturalists, and the names that these men gave them were the ones that stuck." (P. 480)
- "The publication of the Thwaites edition of the journals at the end of the century began a revival. It has continued, and the reputations of the captains have soared." (P. 484)

Blood Test Flags Agent In Death of Penn Subject

Exactly what killed Jesse Gelsinger, the first volunteer to die in a human gene therapy trial, remains a mystery, but last week researchers in Germany fingered a feature of his immune system as a prime suspect. They also believe that a simple blood test might be able to prevent similar tragedies in future gene therapy trials.

In September 1999, 18-year-old Jesse Gelsinger took part in a trial designed to test the safety of using a form of adenovirus to transport new genes into patients. Adenovirus normally only causes mild colds. Nonetheless, within hours of the injection of the virus "vector," Gelsinger's immune system went into overdrive. Four days later he died of multiple organ failure. James Wilson, leader of the trial and head of the Institute for Human Gene Therapy at the University of Pennsylvania in Philadelphia, initially suggested that another viral infection or undetected genetic condition might have triggered the harsh immune response to the adenovirus that investigators concluded had killed Gelsinger (*Science*, 17 December 1999, p. 2244, and 12 May 2000, p. 951). After further studies in monkeys, he pointed to the proteins in the coat of the vector as a possible source of the immune response revolt. Wilson was unavailable for comment on the new findings.

Günter Cichon of the Max Delbrück Center for Molecular Medicine in Berlin and his colleagues sought to find out how adenovirus provokes the body's defenses. They mixed blood samples from 18 individuals with adenovirus that was "externally identical" to the one used in Wilson's trial. The virus set off a forceful response from the complement system, a natural and powerful defense against invading pathogens, but only in samples that already contained antibodies against adenovirus. Reporting in the current issue of *Gene Therapy*, the team concludes that a viral dose comparable to the one Gelsinger received raised the con-

WHY DID JESSE GELSINGER DIE?

centration of a key component of the complement system to a level that could start a damaging immune reaction.

Cichon notes that Gelsinger was known to have "suffered a chest infection some time before the trial," so his complement system might have been sensitized already. In the bloodstream, the proteins of the virus coat would combine with antibodies, forming complexes that activate the complement system. This can cause inflammation in the vessel walls of liver, lungs, and kidney, and ultimately multiple organ failure. "Exactly the same symptoms were observed in the case of Gelsinger," says Cichon.

Gene therapist Prem Seth of Des Moines University in Iowa thinks that complement activation could indeed cause some of the adverse reactions observed in gene therapy trials with adenovirus vectors. Several years ago, he observed that the coat proteins of the virus initiate a strong immune response in human blood. "I have always argued that the virus should only be applied locally, not into the bloodstream," he told *Science*. And he agrees with Cichon that complement activation should be measured in blood samples to see if the test can predict which patients are likely to suffer strong adverse reactions. "All patients should be screened for their complement response," he says. "It is an easy test."

Phil Noguchi, director of the Food and Drug Administration (FDA) division for gene therapy, agrees that this finding is "a new piece in the puzzle" but emphasizes that the fatal trial probably had "multiple sources." He says that the FDA is considering how to use a complement-sensitivity test in gene therapy trials. —ADAM BOSTANCI

Science
25 Jan 2002
295:604-605

CAN THE SCIENTIFIC
METHOD BE USED TO
PREVENT THIS IN THE
FUTURE?