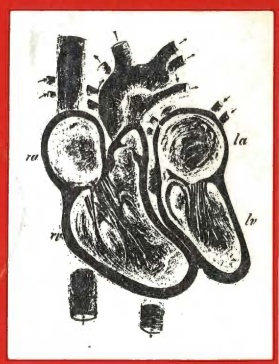
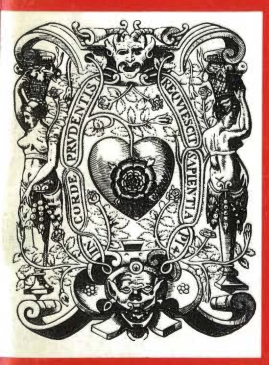
# MCV/Q

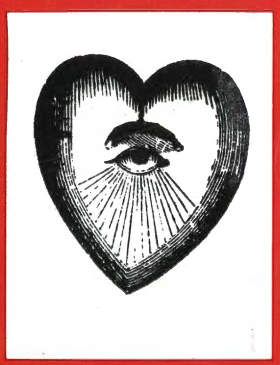
MEDICAL COLLEGE OF VIRGINIA QUARTERLY

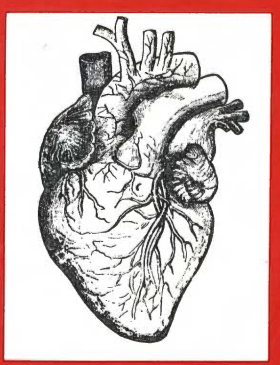
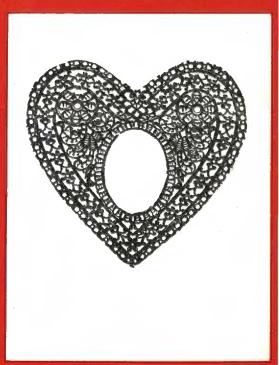
SUMMER 1965







# MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

*A Scientific Publication of the School of Medicine*

SUMMER 1965 • VOLUME ONE • NUMBER TWO


## CONTENTS



## COVER

*The featuring in this issue of several papers on the heart and blood vessels inspired this cover by Jeanne Clark and Raymond Geary. The assortment of scientific, artistic, and romantic representations of the heart is based on; schematic illustration of a congenital anomaly in the pulmonary circulation, eighteenth century insignia of a German printing firm, playing card, symbol for blood bank in Finland, section through a mammalian heart, Renaissance coat of arms, a medieval woodcut, ancient mystic design of four hearts forming a cross, seventeenth century anatomical engraving, and a nineteenth century valentine greeting card. (Most sketches were obtained through the courtesy of the Bettmann Archives, New York.)*

## OPPOSITE

*Anatomy staff members assist students by videotape presentation. Pre-dissection demonstrations relate form to development and function. (See editorial comment and article relating to revision of curriculum at medical school.)*

## THE NEED FOR CHANGE IN MEDICAL EDUCATION

We have much to be modest about in medical education, despite countless publications, conferences, and a great deal of hard work. Advances in medical science, outstripping advances in medical education, are piling up masses of detail that paralyze our present curricula. Medical school programs, long, unimaginative, and overcrowded, tolerate and encourage mediocrity. Small wonder then that many bright college students find other branches of science or other professions more attractive.

Most of us entered medicine with enormous enthusiasm for learning how to care for sick people, and all of us were dulled by two years of pre-clinical work. Most of our students probably come to medical school for much the same reason. Why then must we blunt their enthusiasm and kill their spirits with a year, or more likely two years, of lectures and laboratories that pay little more than lip service to clinical correlations?

Since medical knowledge obviously will continue to grow, and since the capacity of our crania will just as obviously not keep pace, we must accept the fact that none of us is now, nor will we ever train, the "complete physician." We will do well to graduate a student who can become a good house officer, viz., an adaptable student who may enter his specialty training with some idea of how to learn for himself, how to read and think critically, and how to obtain information from a patient. Only a paragon of students is able to survive a curriculum clogged by vast quantities of unrelated facts, and emerge untouched by mediocrity. These factual details we can afford to leave in books, which is where most faculty members have long since left them anyway, after discovering that they lead to mental constipation or worse. The requirements for becoming a good house officer are not great: the guidance of general principles, a limited number of facts and skills, and much free time in which to think about them. Our present medical schools do not provide such programs.

How then can our present curricula be altered to provide programs marked by excellence? Perhaps this can best be accomplished by profiting from the students' initial enthusiasm for patient care; in other words, by giving them the chance to live medicine and absorb it through patient-centered teaching. From the day they enter medical school, they could spend a third of their time in the classroom, a third on the wards, and a third in research, or, like warty bliggens, for contemplation of "the moon and wheeling constellations." Such teaching would have to be done according to organ systems, rather than by departments, and would require active participation in all years by members of all departments. But, who knows? Under such a program, a student might discover that the basic sciences do have some connection with patient diagnosis and care. He might retain his curiosity and independence of thought, and even achieve a sense of proportion.

A perusal of medical school catalogues shows that most schools now use four years to obtain 33 months of actual instruction. Simultaneous basic science-clinical teaching might make it possible to obtain the same 33 months of instruction in a three-year period. Furthermore, by encouraging independent study, such a teaching program undoubtedly would better prepare a student for his specialty training. Our present medical schools are no longer really medical schools, anyway, but are pre-medical schools. It is during the long years of postgraduate training that a man learns his clinical skills.

The key to tomorrow's medical practice lies, not in the development of better clinical artisans, but in the development of clinicians who can interpret disease through application of the basic sciences. A medical curriculum at a graduate student level, based on patient-centered teaching with strong and continuous basic science correlation, could provide such clinician-scientists.

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# An Approach to Medical Education: The Medical College of Virginia School of Medicine Curriculum*

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*Across the nation, medical schools are re-evaluating their objectives and re-examining their teaching philosophies and methods. Many have already adopted new techniques and discarded old ones. The Medical College of Virginia School of Medicine began its own study of medical education in December, 1958, under the former dean, William F. Maloney. The result has been the elaboration of a new curriculum, first put into effect this past academic year, along with a number of other changes in the educational program.*—Ed.

Until the middle 1950's, change was conspicuously absent in the educational programs of medical schools. The rapid growth of medical knowledge had no counterpart in medical education. One reason for this stasis, which lasted from the time of the Flexner Report to the end of World War II, probably was the concept of medical education as a curriculum (Flexner, 1910). The student took prescribed courses; he spent a number of required hours in the laboratory doing experiments whose results had been attested by previous generations of medical students, and, at a designated time, he began several years of clinical work. Adhering to this schedule and passing all the required examinations earned the student an M.D. degree. Except in isolated medical schools, there was little deviation from this pattern.

Early in 1946, an article in the *Journal of Medical Education* took to task American medical education as it existed then and had existed for 50 years. This article (Sanger and Hurd, 1946), co-authored by W. T. Sanger who was then president of M.C.V., received relatively little attention then. However, the criticisms and corrective measures it contained foretold what would happen five years later at Western Reserve University School of Medicine—the seat of the current revolution in medical education. An examination of this article is crucial to an understanding of the present Medical College of Virginia curriculum and of developments in medical education, in general. These were some of the weaknesses in medical education it named:

1) There is little provision for individual difference in medical education. The medical school curriculum is a lock step. Anyone who falls short of this system is eliminated. This tends to standardize a profession, allowing no room for the student who is "different."

2) Too many short courses are present. As new material is added to the armamentarium of the physician, the medical student receives it as a "new course." The new material often is not soundly organized in relation to existing courses.

3) Unwarranted discrete units of instruction are present. The division between preclinical and clinical instruction is artificial; it cannot be defended on educational grounds.

4) The curriculum is too detailed. The accumulation of centuries of knowledge is added to continuously. New knowledge is not integrated with basic principles.

5) Teaching by departments leads to autonomy; representatives of the departments become increasingly unwilling to participate in integrated instruction, which is essential to effective and permanent learning.

6) Course placement in the curriculum is arbitrary and a product of tradition.

7) New concepts in sociology, psychology, etc., have not found their place in the curriculum.

8) The medical curriculum has become too vocational and too professional.

Anyone familiar with the state of medical education can see readily that most developments during the past fifteen years have focused on correcting these criticisms.

There is an impressive number of schools that have embarked on a critical evaluation and, ultimately, a

* Development of the curriculum has been supported in part by a grant from the Old Dominion Foundation.

change in their educational program. Other than the Western Reserve curriculum, few schools have taken as bold a step as the Medical College of Virginia (Ham, 1959). Stanford University (Stowe, 1959), Northwestern University (Cooper and Prior, 1965), Johns Hopkins (1958), and Boston University (Soutter *et al.*, 1959) implemented unique programs to meet their particular needs. Harvard (Karnovsky, 1955), Duke (Woodhall, 1964), and others have applied the same principles to their medical education programs that have guided their medical science developments (Lee, 1962).

As in laboratory experiments, however, many efforts to revise medical education have failed. The reasons for these failures are probably comparable to reasons for failure in the laboratory —inadequately developed goals, poor preparation, or an environment not conducive to experimentation. In spite of the failures, there probably is not a medical school in the United States that is not now seriously examining its educational program, and seeking efficient and effective ways to its educational goals.

### Changes in Curriculum

After several years of planning by a large number of faculty in a nearly endless array of committees, a curriculum was designed. In this curriculum, the four years of medical school are divided into three sections: MEDICINE 1 (M1) approximates the freshman year of medical school and deals with normal structure, function, growth, and development; MEDICINE 2 (M2) deals with abnormal structure, function, growth, and development; and MEDICINE 3 (M3) deals with the remainder of the clinical work. The four years of medical education can best be described as the study of human biology.

The subject matter committees are organized by body systems as originally recommended. From an initial consideration of the CELL, students move along through RETICULOENDOTHELIAL SYSTEM, MUSCULOSKELETAL, etc., completing M1 with the ENDOCRINE SYSTEM. The subject matter committees are chaired by either a basic science or a clinical teacher, who in turn is responsible to the coordinator of M1. Table 1 shows the organization of M1.

As seen in this table, several unique features are present in this curriculum. MAN AND HIS ENVIRONMENT (M&E) encompasses the entire year. An objective of M&E is to relate the content of the various subject matter committees to clinical material. In this phase of M1, students begin with a general consideration of the role of the physician. After this, they are concerned with the general concept of illness and how this affects the patient. Psychological, social, cultural, and other factors are considered. Accompanying this introductory phase, students are studying the material of the first subject matter committee. It is possible then to devote the remainder of M&E to clinical application of material of the subject matter committee.

Provision in the entire curriculum has been made for FREE TIME AND ELECTIVES. In the first year, during a typical week, students have approximately ten hours of unscheduled time. They are then allowed to pursue any activity. However, the faculty is alert that the students are free, and are instructed to channel that free time into constructive academic pursuits. During the last half of the first year, and all of the ensuing years, four hours of the free time are spent in electives. These electives can be didactic courses, laboratory exercises, research projects under the guidance of a faculty member, or work with a medical practitioner on the faculty or in the community. Students are expected to enroll in electives in the second quarter. Although the present arrangement of the curriculum is not based on departmental lines, electives are offered by departments alone. With each year of operation of the curriculum, more electives will be available. A thesis also will be required prior to completion of M1.

### Other Changes in Educational Program

Concomitant with the development of a curriculum design, other changes have occurred in the educational program.

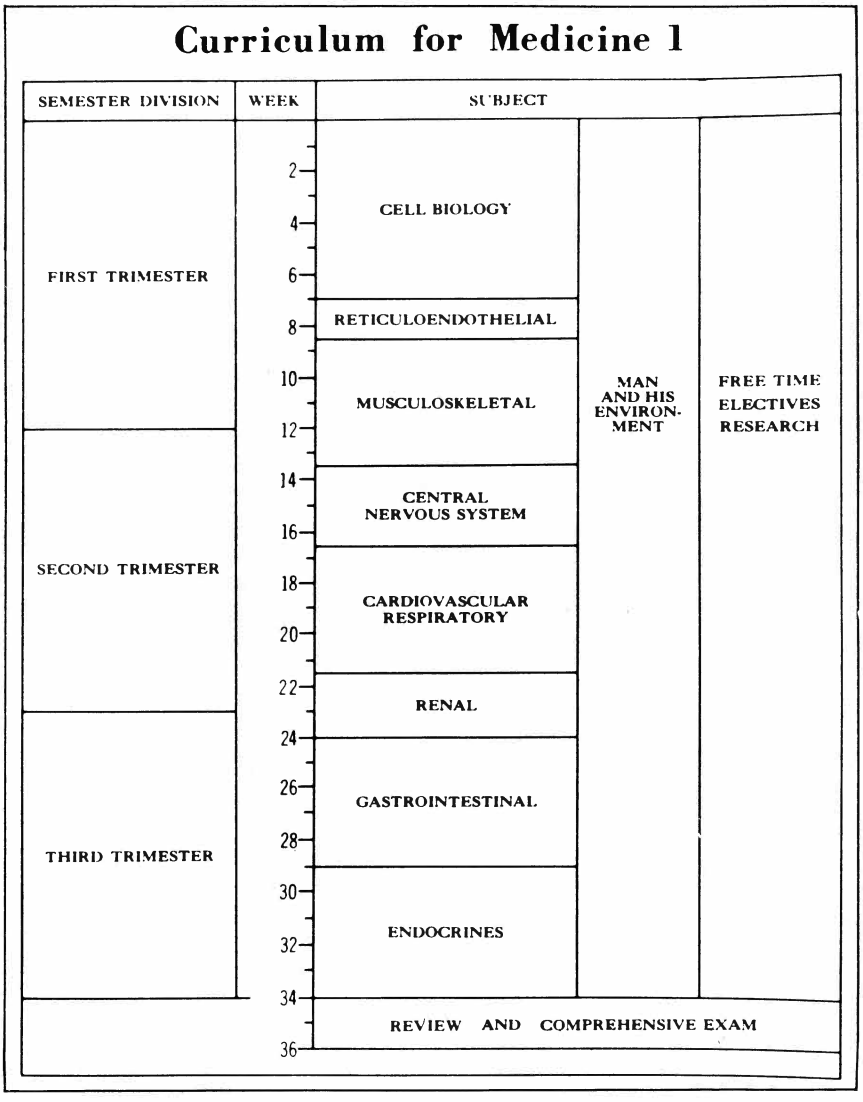
#### *1. Evaluation of Student Performance*

There has been a complete reconsideration of ways to appraise student progress. Previously, measurement of factual knowledge was the focus of nearly all examinations. Now, an evaluation committee, made up of subject matter committee chairmen, considers different techniques to measure all the objectives of the medical school curriculum. A comprehensive examination is given at the end of MEDICINE 1. This examination attempts to measure, in a correlated and integrated manner, material from all subject matter committees. It is the task of the evaluation committee to ensure that the examination does not merely measure isolated pieces of information. Members of this committee have access to consultant help on examination techniques.

#### *2. Grades and Grading Procedures*

With a comprehensive examination, a new system of grading student performance has been introduced. Upon completion of the work in each subject, a student can receive a grade of either *A*, worth 3 quality credits; *B*, worth 2 quality credits; *C*, worth 1 quality credit; *I* (Incomplete), worth no quality credit; or *F*, with a minus 1 credit assigned. An *I* must be removed for promotion to M2. The final comprehensive examination also is graded by the same system. The value of each subject matter committee's grade toward the final grade is based on the per cent of time that subject has been allotted in the total academic year. Therefore, as CELL BIOLOGY represents approximately 11.7% of the teaching time, and RETICULOENDOTHELIAL represents 2.4% of the time, the weight of the total grade is based on this distribution. The following represents the relative weights assigned to each subject matter, and to the comprehensive examination.

| | |
|---|---|
| Cell Biology | 11.7% |
| Reticuloendothelial | 2.4% |
| Musculoskeletal | 9.3% |
| Central Nervous System | 5.7% |
| Cardiovascular-Respiratory | 9.3% |
| Renal | 5.0% |
| Gastrointestinal | 9.3% |




| | |
|---|---|
| Endocrines | 9.3% |
| Man & His Environment | 8.0% |
| | 70 % |
| Comprehensive Examination | 30 % |
| | 100 % |

A final average of *C* is necessary for promotion. Under this system it is possible for a student who has had difficulty in some subjects to bring up his grade by doing well on the comprehensive examination.

### *3. Teaching Methods and Materials*

Anticipating a curriculum revision, a Teaching Materials Committee, in operation for a number of years, began to explore the appropriateness of some newer teaching techniques such as programmed learning, closed circuit television, filmed laboratory experiments, and self-study carrels. Because a major factor in the success of this curriculum depends on the students assuming responsibility for much of their own learning, opportunities for self learning must be provided through the medical school. Many of these opportunities are available, but more need to be instituted.

The choice of teaching methods employed in the curriculum remains with the subject matter committee chairmen and the faculty. Similarly, since the chairmen function as an evaluation committee, they also consider the teaching methods to be used. In the new curriculum, more is done in small groups through conferences, seminars, journal review sessions, and critiques.

### 4. *Studying the Effects of Curriculum Change*

Objective evidence that the newly instituted approach to curriculum approach better achieves the objectives of medical schools has been lacking. Since 1959, when it was anticipated that a curriculum change might occur at the Medical College of Virginia, a committee began to gather comparative data on the old and new curriculums. For five years prior to the curriculum revision, this committee collected data on the student body, faculty, and the effect of the curriculum on the school's objectives. This study continues. In another four years, the first objective of comparative evidence of a curriculum change can be documented. Graduates of both curriculums will be included in the study for several years after graduation. The design of this study is beyond the scope of this presentation.

For the Medical College of Virginia, this curriculum is a major step in the improvement of its educational program. The revision of courses of study is only a part of the educational program, for the faculty defined curriculum as "the total educational experience of the medical student." In addition, this school will be guided by the statement in the last paragraph of the schools' objectives: " . . . the methods of attaining these objectives are not static. The curriculum itself should contain the machinery for frequent critical review and re-evaluation by the faculty and student body."

## Summary

After a relatively long interval in which the status quo was maintained, in the early 1950's American medical schools began to reappraise their educational programs. Many shortcomings of medical education which now have been corrected were cited as early as 1946.

The Medical College of Virginia began a detailed study of its educational program. A curriculum has been designed and initiated, using the subject matter committee approach. The curriculum provides opportunity for electives, research, and free time.

In conjunction with the revised curriculum, changes in grading procedures, examinations, and teaching methods have been made. A study to assess the effects of the change in curriculum also has been designed, and the entire program is under constant study to allow for additional changes as they become necessary.

## References

A revised program of medical education at Johns Hopkins. *J. Med. Educ.* 33: 225–233, 1958.

COOPER, J. A. D., AND M. PRIOR. New program in medical education at Northwestern University. *J. Med. Educ.* 36: 80–90, 1965.

FLEXNER, A. *Medical Education in the United States and Canada.* New York: The Carnegie Foundation for the Advancement of Teaching, 1910.

HAM, T. H. The approaches of the faculty to medical education at Western Reserve University. *J. Med. Educ.* 34: 1163–1174, 1959.

KARNOVSKY, M. L. A unified approach to the basic medical sciences at Harvard. *J. Med. Educ.* 30: 15–24, 1955.

LEE, P. V. *Medical Schools and the Changing Times*, Evanston, Ill.: Association of American Medical Colleges, 1962.

SANGER, W. T., AND A. W. HURD. What the educator thinks the ideal medical curriculum should be. *J. Assoc. Am. Med. Colleges* 21: 8–18, 1946.

SOUTTER, L., J. P. MASON, R. M. MILLARD, AND D. I. PATT. *A New Combined Liberal Arts—Medical Program of Medical Education.* Report of Joint Committee, Boston University, 1959 (cited by Lee, 1962, p. 28).

STOWE, L. M. The Stanford plan: An educational continuum for medicine. *J. Med. Educ.* 34: 1059–1069, 1959.

WOODHALL, B. Deans corner. *Duke Med. Alumni Newsletter* Spring: 2–3, 1964.

## What Motivates a Medical Student?

"Traditionally, the term motivation has also been used in psychology in another way; to account not only for the degree of activity a person manifests but also for the fact that he moves in certain directions rather than others. This definition seems more in keeping with the connotation of the term as it is used in the procedure for selecting medical students. Here it is usually phrased as 'motivation toward a career in medicine' or 'motivating factors leading to the choice of medicine.' Some like to believe that the two kinds of motivation are intimately related, but contemporary research makes this appear unlikely. Strictly speaking, the term motivation is not a felicitous one to use in discussing reasons for the choice in terms of 'personal values' or 'orientations.' This does not imply that an appraisal of the applicant's value systems or orientations is unsuitable in the selection process. It does imply, however, that the members of an admissions committee who concern themselves with this problem have identified certain values that they prize more highly than others in prospective physicians. It implies that without tangible evidence as to what makes a good physician, they have decided that they prefer to see in the candidate an interest in helping people rather than in making money, or an interest in medical research rather than in attaining a position of great social prestige or domination.

"A student questioned on these points quickly recognizes that values are involved. It is very possible that he is not aware of all the determining factors that led him to this choosing point in the development of his career, but Christie (Christie, R. *The Physician's Perception of His Role.* Paper read at meeting of the Eastern Psychological Association, Atlantic City, April, 1959) reports that the typical applicant, when asked why he chose to enter medicine, usually responds first in terms of helping people. If he is then asked what he would choose if he were not accepted into medical school, he does not pick a 'people' field such as social science or clergy, but rather a science field like chemistry or biology. Several hypotheses can be suggested to account for this sequence, but certainly one is that the applicant is trying to match his responses with what he believes is expected of him. The medical profession appears to value a service orientation highly, and the candidate who does not fit this pattern may find his chances for admission to apprenticeship lessened. At the same time, analyses of contemporary American society show a predominant achievement orientation (accumulation of money, of things, of status), and if the student is a good representative of the society in which he lives this orientation probably affects his own value system. Should he then reflect this society and lessen his chances for admission, or should he respond in the way which appears to be expected? Should the medical school select chiefly those who are atypical of the society from which they come (with the consequent problem of a markedly reduced pool from which to select) or those who are able to mouth the appropriate responses without necessarily endorsing them? Or should the school take the best possible candidates, on the basis of other criteria, and attempt to develop what they perceive to be an appropriate professional orientation during the subsequent training? This dilemma of values the medical profession, through the selection committees of its professional schools, must face realistically. Until it does, the applicant who responds as he feels he is expected to respond is probably showing good judgement. If he were to do otherwise, the selection committee might reasonably question his social sensitivity and judgement, if not his 'motivation for medicine.' "

George E. Miller, ed. *Teaching and Learning in Medical School.* Cambridge, Mass.: Harvard University Press, 1961, pp. 12–13.

# Physiological Basis of the Radioisotope Renogram

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The *renogram*, a test of renal function introduced in 1956 by Taplin *et al.* (1956), is obtained by injecting some substance tagged with radioactivity which accumulates in a relatively selective manner in the kidney. Collimated counters placed over the two kidneys measure the accumulation of radioactivity, and its subsequent decrease. When the counter is connected to automatic recording devices, the curves produced begin at the origin, rise rapidly to a peak, and then fall in an approximately exponential manner. (fig. 3)

Blaufox, Orvis, and Owen (1963) have done a compartment analysis of Hippuran $I^{131}$ in dogs and have suggested that characteristics of the radioisotope renogram may be elucidated by compartment analysis. The present paper is based on a similar compartment analysis. A different model, however, is proposed to describe the renogram. Estimates of the parameters are obtained by the *method of maximum likelihood* rather than by graphical means. In addition, certain implications and possible application of the model, not discussed by Blaufox *et al.*, are developed here.

* Work supported in part by NIH 3676 and by NIH training grant 2G-693. Submitted in partial fulfillment of the requirements for an M.D. degree at the Medical College of Virginia, Richmond, Va.

† This work done in part during term of a World Health Organization fellowship. Opinions expressed are not necessarily those of the World Health Organization.

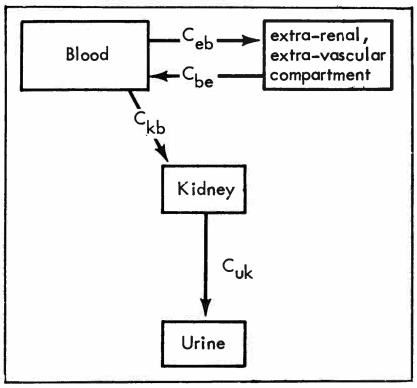


Fig. 1—Ortho-iodohippuran is imagined to mix very rapidly in the blood, and exchange with a non-vascular, non-renal space. It is assumed that a constant fraction of circulating hippuran is removed from the blood by the kidneys per unit time.

The compartment analysis to be done is schematized in figure 1. Berman, Weiss, and Shahn (1962) have published a general treatment of compartment analysis. Sapirstein *et al.* (1955) have proposed the particular analysis used here in deriving the blood curve for use in renal physiology.

## The Blood Curve

Assume the injected substance is distributed principally into four compartments during the 20 minute duration of the experiment. These compartments are the blood, kidney, urine, and an extravascular, extrarenal space, and are designated by the subscripts $b$, $k$, $u$, and $e$, respectively. It is also assumed that:

a) Intravascular mixing takes place very rapidly, compared to exchanges between other compartments.
b) Compartment $u$ exchanges only with $k$, $k$ only with $b$ and $u$, and $e$ only with $b$.
c) The volumes of compartments $b$, $k$, and $e$ are each constant.

We may write:

$$v_b\dot{Y}_b = -C_{kb}Y_b + C_{be}(Y_e - Y_b), \quad (1)$$

$$v_e\dot{Y}_e = C_{be}(Y_b - Y_e), \quad (2)$$

where:

$v_i$ = volume of compartment $i$,
$C_{ij}$ = the volume of compartment $j$ cleared per unit time with transfer to compartment $i$. No assumptions are made concerning mechanisms of clearance except that $C_{be} = C_{eb}$; that is, there is no asymmetry of mechanism between compartments $e$ and $b$.
$Y_i$ = concentration of the injected substance in compartment $i$.

$\dot{Y}_b$ and $\dot{Y}_e$ are time derivatives of $Y_b$ and $Y_e$, respectively. Equations (1) and (2) are satisfied by

$$Y_b = B_{1b}\exp(\gamma_1 t) + B_{2b}\exp(\gamma_2 t) \quad (3)$$

where $t$ is time, and $B_{1b}$ and $B_{2b}$ are constants chosen to satisfy the initial conditions. $\gamma_1$ and $\gamma_2$ are the roots of a quadratic equation,

$$x^2 + ((C_{kb}/V_b) + (C_{be}/V_b) + (C_{be}/V_e))x + (C_{be}C_{kb})/(V_eV_b) = 0 \quad (4)$$

The choice of a two-compartment system to describe the blood curve is based on the suggestion of previous workers (Sapirstein *et al.*, 1955) but is here merely illustrative. More general systems might be used instead, and appropriate modifications made in the development which follows.

### The Renogram

We consider the total kidney count exclusive of contribution from other tissues over one kidney, $y_r$ to be given by:

$$y_r = C_{kb}' \int_{\tau}^{t} Y_b(s)ds \qquad (5)$$

where $s$ is a time variable of integration
$C_{kb}'$ is the unilateral clearance, assumed to be constant.

$$\tau = \begin{Bmatrix} 0 \text{ for } 0 \leq t < a \\ t - a \text{ for } a \leq t \end{Bmatrix}$$

$a$ is the appearance time of ortho-iodohippuran in the kidney.

The choice of limits of integration in (5) means that we imagine $y$ to be simply accumulating within the kidney until $t - a$. At that time, $y$ begins leaving the kidney and appears in the urine. If there is little or no longitudinal mixing of urine within the tubules, the successively excreted quantities of $y$ in the urine will be just those quantities filtered $t - a$ minutes ago. Imagine an infinitely long train of microscopic box cars, each filled with an amount of $y$ proportional to $y_b$ as it enters the kidney. It takes each box car "$a$" minutes to leave the kidney. Thus if we want to measure $y$ at some $t \geq a$, we sum up all the $y$ which has entered, and subtract all that came in box cars which entered at some time, $t - a$, and has now left the kidney. That is,

$$y_R = C_{kb}' \left( \int_0^t y_b - \int_0^{t-a} y_b \right) \cdot ds, \; t \geq a, \qquad (6)$$

or

$$y_R = C_{kb}' \int_{t-a}^{t} y_b ds, \; t \geq a. \qquad (7)$$

If we substitute (3) into (5), and integrate, we obtain for $t \geq a$,

$$y_R = A_{1R} \exp(\gamma_1 t) + A_{2R} \exp(\gamma_2 t) \qquad (8)$$

$A_{1R}$ and $A_{2R}$ are constants determined by $C_{kb}'$, $\gamma_1$, $\gamma_2$, $B_{1b}$, and $B_{2b}$. Since, in fact, we may count over tissue and blood as well as over kidney, the counting device will record,

$$Y_R = \alpha_1 y_b + \alpha_2 y_e + \alpha_3 y_R + \alpha_4 y_u \qquad (9)$$

where $\alpha_i$ are constants determined by the positioning of the detector, and the proportion of each compartment will appear in the counting field. $Y_R$, however, is still a linear combination of the same exponential terms. So we may rewrite (9) as

$$Y_R = B_{1R} \exp(\gamma_1 t) + B_{2R} \exp(\gamma_2 t) \qquad (10)$$

$B_{1R}$ and $B_{2R}$ are constants.

### The Urine Curve

Since the ortho-iodohippuran removed from the blood appears a short time later in the urine, we write

$$(C_{uk} y_u)_t = (C_{kb}' y_b)_{t-a}, \qquad (11)$$

where $C_{uk}$ is the urine flow rate. Sodium ortho-iodohippurate excretion (mg per minute) at time $t$ is simply equal to the sodium ortho-iodohippurate cleared by the kidney (mg per minute) at $t - a$. The blood curve is evaluated at $t - a$ to predict the urine curve at $t$.

$$C_{uk} y_u = C_{kb}' \{ B_{1b} \exp[\gamma_1 (t - a)] + B_{2b} \exp[\gamma_2 (t - a)] \}, \qquad (12)$$

For convenience we rewrite (12) as

$$Y_u = C_{uk} y_u = B_{1u} \exp(\gamma_1 t) + B_{2u} \exp(\gamma_2 t) \qquad (13)$$

### Experimental Methods

Experiments were performed on dogs anesthetized with intravenous sodium pentobarbital (30 mgm per kg body weight). Additional doses of anesthetic were given during the experiment as needed. Respiration was maintained with a motor-driven pump following intratracheal intubation. During the preparatory period and throughout the experiment, the animals received a constant intravenous infusion of isotonic saline, or a mixture of equal volumes of isotonic saline and 5% dextrose in water.

Renograms were obtained with a pair of matched scintillation counters (1 x 1 inch thallium-activated sodium iodide crystals), connected to pulse-height discriminators, ratemeters, and a dual linear recorder. A time constant of 10 seconds, and a full-scale setting of 10,000 counts per minute, were employed. All records were obtained with a paper speed of 12 inches per hour. The tracings were allowed to run for 15–20 minutes.

The radioactive material used was $I^{131}$-labeled sodium ortho-iodohippurate (Hippuran®), obtained from Abbott Laboratories. All renograms were obtained by injecting within 5 seconds 1.5 mc of radioisotope per kg body weight into the vein of a forelimb.

The experimental procedure was as follows: The animal was placed in the supine position and the peritoneal cavity was entered through a midline incision. The ureters were identified, divided at their upper part and their proximal, and cannulated with polyethylene tubing. To minimize dead space, the length of ureteral catheters was kept short and their tips were introduced into or very near to the renal pelvis. Then the right renal artery was dissected free and a Crutchfield clamp was placed around it without constricting the vessel. When urine flow became constant, the probes were placed immediately overlying the exposed kidneys, and control renograms were obtained. The position of the probes remained the same throughout the experiment.

Aortic blood was sampled through a catheter placed into the lower aorta, at 15 second intervals for the first 3 minutes following the injection of iodohippurate, and at 30 second intervals, subsequently. All urine excreted during the inscription of the renogram was collected. Collection periods lasted 15 seconds for the first 3 minutes following the administration of the radioisotope, and 30 seconds, subsequently.

Blood and urine specimens were counted in a scintillation-well counter, for periods long enough to give standard deviations not exceeding 1%. Background and blank counts were subtracted from each count rate.

The urine count rate per second of each specimen was divided by the duration of the period of collection in minutes to obtain the rate of excretion of radioisotope per minute. The data from

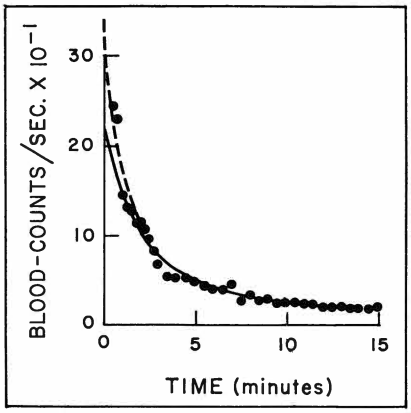


Fig. 2—Counts/sec in 1 ml of blood at various times after injection of $I^{131}$ ortho-iodohippuran. Observed values are shown as points. Estimated values computed as $\hat{Y}_{bj}$ of Table 2 shown by dotted line. Solid line obtained as $\hat{Y}_{bj}(H_0)$ of table 2.

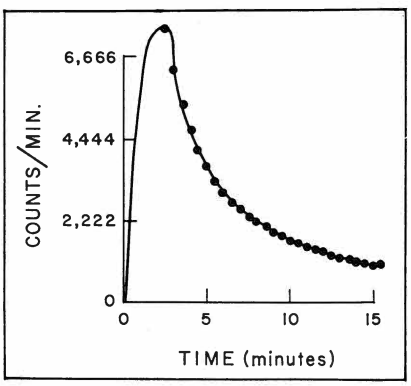


Fig. 3—The renogram from which the points shown in table 3 were obtained. Circled points are the estimates labeled $\hat{Y}_{Rj}(H_0)$ in table 3. The estimates labeled $\hat{Y}_{Rj}$ actually fit somewhat better, but this is not apparent graphically.

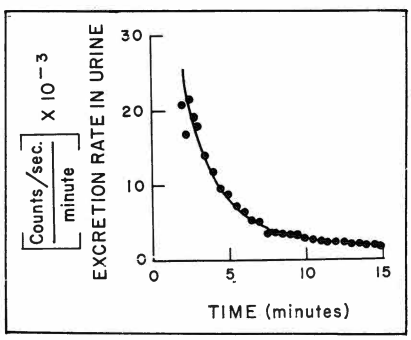


Fig. 4—Observed and estimated (counts/sec) $\times 10^{-3}$ excreted per minute at various times following the injection of $I^{131}$ ortho-iodohippuran. Points are taken from $Y_{uj}$ of table 4. The solid line is estimated in the same manner as $\hat{Y}_{uj}(H_0)$ of table 4.

one such experiment is used in this analysis.

### Estimation Procedures

The data obtained for estimating the blood curve (equation 6) consists of $N_b$ points $(1, 2, \cdots, j, \cdots, N_b)$ recorded in counts per ml at successive time points $(t_1, t_2, \cdots, t_j, \cdots, t_{N_b})$.

$$Y_{bj} = B_{1b} \exp(\gamma_1 t_j) + B_{2b} \exp(\gamma_2 t_j) + \epsilon_{bj}\phi_b(t_j), \tag{14}$$

$Y_{bj}$ = counts/ml at time $t_j$, and
$\epsilon_{bj}\phi_b(t_j)$ = "error;" the $\epsilon_{bj}$ are taken to be normally and independently distributed with mean zero and constant variance (for the blood curve) $\sigma_b^2$.

For the points on the descending portion of the renogram curve we have

$$Y_{Rj} = B_{1R} \exp(\gamma_1 t_j) + B_{2R} \exp(\gamma_2 t_j) + \epsilon_{Rj}\phi_R(t_j), \tag{15}$$

$\epsilon_{Rj}\phi_R(t_j)$ is as before the error; the $\epsilon_{Rj}$ are also taken to be normally and independently distributed with mean zero and constant variance $\sigma_R^2$. Because of the 10 second response time of the recorder, and the extremely rapid rise of the renogram curve in its initial phase, it was decided that this portion of the curve was unsuitable for analysis, and only the portion after the peak was used.

The urine data is in counts/min per minute of urine flow. Each datum has the dimensions of $(C_{uk}y_u)$.

$$y_u = \text{concentration of counts in the urine}$$
$$Y_{uj} = (C_{uk}y_u)_j + \epsilon_{uj}\phi_u(t_j), \tag{16}$$

$\epsilon_{uj}\phi_u(t_j)$ is the error and $\epsilon_{uj}$ has variance $\sigma_u^2$, but is otherwise like $\epsilon_{bj}$ and $\epsilon_{Rj}$.

Equations (14), (15), (16) may be summarized as follows:

$$Y_{ij} = B_{1i} \exp(\gamma_1 t_j) + B_{2i} \exp(\gamma_2 t_j) + \epsilon_{ij}\phi_i(t_j); \tag{17}$$
$$i = b, R, u;$$
$$j = 1, 2, \ldots, N_i;$$
$$\phi_i(t_j) = \hat{\hat{y}}_{ij}$$

We will estimate the parameters by the method of maximum likelihood (5). The likelihood function is proportional to

$$e^L = \prod_{i=b}^{u} \prod_{j=1}^{Ni} (2\pi\phi_{ij}^2\sigma_i^2)^{-1/2} \cdot \exp\{-[\epsilon_{ij}\phi_i(t_j)]^2/2\phi_{ij}^2\sigma_i^2\}. \tag{18}$$

$\hat{Y}_{ij}$ is the estimated value of $Y$ at $t_j$ using the maximum likelihood estimates of the parameters appearing in equation (17). Taking the log of (18), and substituting into it $\epsilon_{ij}$ from (17), we obtain

$$L = \sum_{i=b}^{u} \sum_{j=1}^{Ni} (-\tfrac{1}{2} \log[2\pi\phi_{ij}^2\sigma_i^2]) - (Y_{ij} - B_{1i} \exp[\gamma_1 t_j] - B_{2i} \exp[\gamma_2 t_j])^2/2\phi_{ij}^2\sigma_i^2 \tag{19}$$

In order to find those estimates of the parameters which maximize $L$ we take

$$0 = \partial L/\partial\gamma_1 = \partial L/\partial\gamma_2 = \partial L/\partial B_{1i} = \partial L/\partial B_{2i}.$$

Papers on fitting equations of compartment analysis have been published by Berman, Shahn, and Weiss (1962), and Berman. A more general approach, of which this problem is a special case, has been made by Turner, Monroe, and Homer (1963). Because equation (14) is non-linear in $\gamma_1$ and $\gamma_2$, these parameters must be estimated by an iterative procedure. The procedure used in the illustration presented here was as follows:

a) use trial values of $\hat{\phi}_{ij}$, $\hat{\gamma}_1$, $\hat{\gamma}$.
b) estimate $\hat{B}_{1i}$ and $\hat{B}_{2i}$.
c) obtain new estimate of $\hat{\phi}_{ij} = \hat{y}_{ij}$
d) obtain new trial values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$.
e) Repeat the previous steps until one finds a $\hat{\gamma}_1$ and $\hat{\gamma}_2$ for which the sum of the squared errors given by

$$\sum_{j=1}^{Ni} = (\epsilon_{ij}\phi_i(t_j))^2 = SSE_i \tag{20}$$

is lower than for other values of $\gamma_1$ and $\gamma_2$ in the neighborhood of $\hat{\gamma}_1$ and $\hat{\gamma}_2$.

The best values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$ are found by this procedure for the blood, renogram, and urine, separately. When estimating one curve at a time, no value need be assigned to $\sigma_i^2$. After the best values of the parameters $B_{1i}$, $B_{2i}$, $\gamma_{1i}$, $\gamma_{2i}$ have been obtained, $SSE_i$ may

be computed, and an estimate of $\sigma_i^2$ is given by

$$\sigma_i^2 = SSE_i/(N_i - 4) \qquad (21)$$

Using the combined data to find the values of $\gamma_1$ and $\gamma_2$ which give the best fit for all three sets of data at once requires a slightly different procedure. First of all, as can be seen from equation (19), $\sigma_i^2$ is required. An alternative is to use estimates of $\sigma_i^2$ given by (21). This alternative introduces a substantial simplification into the numerical procedure at a cost of some information. $\phi_{ij}$ is kept constant instead of being re-estimated after each iteration as is done when analyzing the data separately. The values chosen are those used in the last iteration on each separate curve. This restriction is necessary in order to be able to compare $SSE_i$ obtained using the combined estimates of $\gamma_1$ and $\gamma_2$. Finally a new criterion of fit must be chosen. The best pair of $\gamma$'s for the combined data was that pair which minimized the weighted least squares criterion $S$, given by

$$S = \sum_{i=b}^{u} SSE_i'/\hat{\sigma}_i^2, \hat{\sigma}_i^2 = SSE_i/(Ni - 4);$$

$SSE_i$ is the sum of the squared errors for $i$ set of data using the best separate values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$, and $SSE_i'$ is the sum of the squared errors for $i$ set of data using the best values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$ from the combined data.

A program was written for the RPC 4000 computer to perform the calculations described, and to print out the estimates of the parameters, $SSE_i$ and $R^2$. $R^2$ may be interpreted as the percentage of variation in $Y_i$, which can be accounted for by the hypothesis calculated by

$$R_i^2 = 1 - SSE_i \Big/ \left\{ \sum_{j=1}^{Ni} Y_{ij}^2/\phi_{ij}^2 - \left( \sum_{j=1}^{Ni} Y_{ij}/\phi_{ij}^2 \right)^2 \Big/ \left( \sum_{j=1}^{Ni} \frac{1}{\phi_{ij}^2} \right) \right\} \qquad (22)$$

## Results

The data, estimates of parameters and estimates of $Y_{ij}$, are given in tables 1 to 4 and figures 2 to 4.

An approximate $F$ test may be devised to test the hypothesis that $\gamma_{1b} = \gamma_{1k} = \gamma_{1u}$, and at the same time, that $\gamma_{2b} = \gamma_{2k} = \gamma_{2u}$. Using our previous notation, we have

TABLE 1

Estimates of the parameters and statistics measuring goodness of fit, $\hat{B}_1$, $\hat{B}_2$, $\hat{\gamma}_1$, and $\hat{\gamma}_2$ have the same meaning as in the text. Estimates obtained from fitting the $\gamma$'s with pooled data and assuming $\gamma_{1b} = \gamma_{1k} = \gamma_{1u}$, and at the same time that $\gamma_{2b} = \gamma_{2k} = \gamma_{2u}$, are in the second line of each pair.

| | $\hat{B}_1$ | $\hat{B}_2$ | $\hat{\gamma}_1$ | $\hat{\gamma}_2$ | Sums of Squares due to Error | Coefficient of Determination | No. of Observations |
|---|---|---|---|---|---|---|---|
| Blood | 26.21 | 6.25 | −.8178 | −.0893 | 31.14 | .967 | 35 |
| | 15.94 | 6.42 | −.5517 | −.0979 | 58.28 | .939 | 35 |
| Renogram | 58.45 | 19.60 | −.4915 | −.1001 | 3.462 | .994 | 27 |
| | 72.94 | 19.47 | −.5517 | −.0979 | 4.267 | .992 | 27 |
| Urine | 47.50 | 3.60 | −.4337 | −.0489 | 15.32 | .982 | 29 |
| | 55.27 | 7.22 | −.5517 | −.0979 | 18.74 | .978 | 29 |

$$F = \left\{ \left[ \left( \sum_{i=b}^{u} SSE_i'/\hat{\sigma}_i^2 \right) - \left( \sum_{i=b}^{u} SSE_i/\hat{\sigma}_i^2 \right) \right] \Big/ 4 \right\} \Big/ \left( \sum_{i=b}^{u} SSE_i/\hat{\sigma}_i^2 \right) \Big/ 79 = 9.5$$

with 4 and 79 degrees of freedom. We may reject the hypothesis with greater than 99.9% confidence ($P < .001$), in favor of a hypothesis in which some or all of the $\gamma$'s are different. Attention is called to the high values of $R^2$. While fitting the $\gamma$'s separately gives a significantly better fit, it is not much better from the standpoint of the value of $R^2$. The worst fit found has an $R^2$ of 0.94. Examination of tables 1 to 3 shows that, except for perhaps the first 5 points on the blood curve, the estimates of $Y_i$ obtained with $\gamma$'s from pooled data are very close to those obtained with the separately estimated $\gamma$'s. Although the differences are quite significant, they are rather small. We can be relatively sure that the $\gamma$'s differ but the differences may not be important.

## Discussion

Clinical investigators have attempted to characterize the renogram by measuring the height of the maximum, the time of the maximum, and the "half time" of the descending slope (Stewart and Haynie, 1962). Our model predicts that these measurements are not related in any simple fashion to either the bilateral or unilateral renal clearance of ortho-iodohippurate. According to the model, the height of the maximum, disregarding contribution from other tissues, will be given by

$$Y_R(\max) = C_{kb}'\{ - (B_{1b}/\gamma_1 + B_{2b}/\gamma_2) + [B_{1b} \exp(\gamma_1 a)/\gamma_1 + B_{2b} \exp(\gamma_2 a)/\gamma_2]\}/v_k,$$

from equations (14) and (15). This maximum will depend on renal blood flow since $C_{kb}'$ should approximate unilateral renal blood flow. $Y_R(\max)$ will also depend on the appearance time and bilateral renal blood flow. The relationship of the maximum and the appearance time to bilateral and unilateral clearance is not a simple one. For example, $Y_R(\max)$ might be unchanged in spite of a decrease in unilateral clearance if the appearance time were prolonged. The time required for the renogram to fall from its maximum to one-half the maximum is often referred to as the half-time of the renogram. Since the proposed hypothesis describes the renogram as the sum of two exponential functions, no simple interpretation of the meaning of this half time is possible in terms of the fundamental parameters.

Ortho-iodohippurate clearances are considered rather direct measures of renal blood flow. A scheme for analysing

**TABLE 2**

Observed and estimated counts/sec-ml in the blood at $t_j$ minutes after injection of $I^{131}$ ortho-iodohippuran. $Y_{bj}$, $\hat{Y}_{bj}$, and $\hat{Y}_{bj}(H_0)$ are reported in counts/sec $\times 10^{-1}$ for one ml of blood. $Y_{bj}$ are the observed values. $\hat{Y}_{bj} = \hat{B}_{1b} \exp(\hat{\gamma}_1 t_j) + \hat{B}_{2b} \exp(\hat{\gamma}_2 t_j)$ where $\hat{B}_{1b}$, $\hat{B}_{2b}$, $\hat{\gamma}_1$, and $\hat{\gamma}_2$ are taken from the top line of table 1. $Y_{bj}(H_0)$ is computed as $Y_{bj}$ except that $B_{1b}$, $B_{2b}$, $\gamma_1$, and $\gamma_2$ are taken from the second line of table 1.

| $t_j$ | $Y_{bj}$ | $\hat{Y}_{bj}$ | $\hat{Y}_{bj}(H_0)$ |
|---|---|---|---|
| 0.5 | 24.3 | 23.4 | 18.2 |
| 0.75 | 22.9 | 20.0 | 16.5 |
| 1.0 | 14.3 | 17.3 | 15.0 |
| 1.25 | 13.2 | 15.0 | 13.7 |
| 1.5 | 12.9 | 13.2 | 12.5 |
| 1.75 | 11.2 | 11.6 | 11.48 |
| 2.0 | 11.4 | 10.3 | 10.57 |
| 2.25 | 10.6 | 9.27 | 9.76 |
| 2.5 | 9.5 | 8.39 | 9.04 |
| 2.75 | 7.1 | 7.65 | 8.40 |
| 3.0 | 6.5 | 7.03 | 7.83 |
| 3.5 | 5.2 | 6.07 | 6.87 |
| 4.0 | 5.0 | 5.37 | 6.09 |
| 4.5 | 5.1 | 4.84 | 5.46 |
| 5.0 | 4.7 | 4.44 | 4.94 |
| 5.5 | 4.2 | 4.11 | 4.51 |
| 6.0 | 3.9 | 3.85 | 4.15 |
| 6.5 | 3.9 | 3.63 | 3.84 |
| 7.0 | 4.3 | 3.43 | 3.57 |
| 7.5 | 2.8 | 3.25 | 3.34 |
| 8.0 | 3.1 | 3.10 | 3.13 |
| 8.5 | 2.8 | 2.95 | 2.94 |
| 9.0 | 2.9 | 2.81 | 2.77 |
| 9.5 | 2.3 | 2.69 | 2.62 |
| 10.0 | 2.5 | 2.56 | 2.48 |
| 10.5 | 2.5 | 2.45 | 2.34 |
| 11.0 | 2.2 | 2.34 | 2.22 |
| 11.5 | 2.2 | 2.24 | 2.11 |
| 12.0 | 2.0 | 2.14 | 2.00 |
| 12.5 | 2.0 | 2.05 | 1.90 |
| 13.0 | 2.0 | 1.96 | 1.81 |
| 13.5 | 1.8 | 1.87 | 1.72 |
| 14.0 | 1.8 | 1.79 | 1.64 |
| 14.5 | 1.7 | 1.71 | 1.56 |
| 15.0 | 1.9 | 1.64 | 1.48 |

**TABLE 3**

Observed and estimated (counts/min)/222.2 of renogram $t_j$ minutes after injection of $I^{131}$ ortho-iodohippuran. $Y_{Rj}$ are obtained from the renogram in figure 3. $\hat{Y}_{Rj} = \hat{B}_{1R} \exp(\hat{\gamma}_1 t_j) + \hat{B}_{2R} \exp(\hat{\gamma}_2 t_j)$ where $\hat{B}_{1R}$, $\hat{B}_{2R}$, $\hat{\gamma}_1$, and $\hat{\gamma}_2$ are taken from line 3 of table 1. $\hat{Y}_{Rj}(H_0)$ is obtained using the estimates in line 4 of table 1.

| $t_j$ | $Y_{Rj}$ | $\hat{Y}_{Rj}$ | $\hat{Y}_{Rj}(H_0)$ |
|---|---|---|---|
| 2.5 | 32.5 | 32.3 | 33.6 |
| 3.0 | 27.5 | 27.9 | 28.4 |
| 3.5 | 23.8 | 24.2 | 24.4 |
| 4.0 | 22.3 | 21.3 | 21.1 |
| 4.5 | 19.2 | 18.9 | 18.6 |
| 5.0 | 17.0 | 16.9 | 16.6 |
| 5.5 | 14.9 | 15.2 | 14.9 |
| 6.0 | 13.4 | 13.8 | 13.5 |
| 6.5 | 12.4 | 12.6 | 12.3 |
| 7.0 | 11.4 | 11.6 | 11.3 |
| 7.5 | 10.6 | 10.7 | 10.5 |
| 8.0 | 10.2 | 10.0 | 9.8 |
| 8.5 | 9.7 | 9.3 | 9.1 |
| 9.0 | 9.0 | 8.7 | 8.6 |
| 9.5 | 8.4 | 8.1 | 8.1 |
| 10.0 | 7.3 | 7.6 | 7.6 |
| 10.5 | 6.9 | 7.2 | 7.2 |
| 11.0 | 6.6 | 6.8 | 6.8 |
| 11.5 | 6.3 | 6.4 | 6.4 |
| 12.0 | 6.2 | 6.1 | 6.1 |
| 12.5 | 6.0 | 5.7 | 5.8 |
| 13.0 | 5.8 | 5.4 | 5.5 |
| 13.5 | 4.9 | 5.2 | 5.2 |
| 14.0 | 4.7 | 4.9 | 5.0 |
| 14.5 | 4.3 | 4.6 | 4.7 |
| 15.0 | 4.5 | 4.4 | 4.5 |
| 15.5 | 4.4 | 4.2 | 4.3 |

renograms which would permit estimates of these clearances to be made might prove of great clinical value. Using the model presented here, we are able to suggest several different approaches to the analyses of the renogram which should provide such information. While the analyses suggested involve procedures more complicated than merely measuring the "half time," the appearance time, or the height of the maximum, much is to be gained in simplicity of interpretation since the analyses provide estimates of bilateral and unilateral clearances, while no such fundamental information may be easily obtained from the simple measurements referred to above. It is hoped that the more precise and more easily interpreted information thus obtained from the renogram would be of sufficient clinical importance to justify somewhat more complicated analyses than have been previously attempted.

Bilateral renal function may be assessed with $\gamma_1$ and $\gamma_2$. From the relationship of equation (4)

$$\gamma_1\gamma_2 = C_{kb}C_{be}/v_e v_b\,, \qquad (23)$$

$$\partial(\gamma_1\gamma_2)/\partial C_{kb} = C_{be}/v_e v_b\,. \qquad (24)$$

The left member of (24) is always positive so that a decrease in $C_{kb}$ should be reflected in a decrease in $\gamma_1\gamma_2$. Perhaps persons having decreased total renal blood flow will have unusually low values of $\gamma_1\gamma_2$. Also from equation (4) we have,

$$\gamma_1 + \gamma_2 = -(C_{kb}/v_b + C_{be}/v_e + C_{be}/v_b), \qquad (25)$$

$$\partial(\gamma_1 + \gamma_2)/\partial C_{kb} = -\frac{1}{v_b} \qquad (26)$$

As $C_{kb}$ decreases, $\gamma_1 + \gamma_2$ increases (becomes less negative). Thus, in general, persons with low renal blood flows might be expected to have values of $\gamma_1 + \gamma_2$, less negative than persons with higher renal blood flows.

The two parameters $\gamma_1$ and $\gamma_2$ could be determined in "normal" patients, and changes in $\gamma_1\gamma_2$ and $\gamma_1 + \gamma_2$ might be simply interpreted as changes in clearance. If the blood curve were also determined, it would be possible to obtain numerical estimates of bilateral renal blood flow, compartment volumes, and compartment exchange rates, using

**TABLE 4**

Observed and estimated (counts/sec) $\times 10^{-3}$ excreted each minute in the urine $t_j$ minutes after the injection of $I^{131}$ ortho-iodohippuran. $\hat{Y}_{uj}$ are the observations. $\hat{Y}_{uj} = \hat{B}_{1u} \exp(\hat{\gamma}_1 t_j) + \hat{B}_{2u} \exp(\hat{\gamma}_2 t_j)$ where $\hat{B}_{1u}$, $\hat{B}_{2u}$, $\hat{\gamma}_1$, and $\hat{\gamma}_2$ are taken from line 5 of table 1. $\hat{Y}_j(H_0)$ was calculated using the estimates in the last line.

| $t_j$ | $Y_{uj}$ | $\hat{Y}_{uj}$ | $\hat{Y}_{uj}(H_0)$ |
|---|---|---|---|
| 2.0 | 20.8 | 23.2 | 24.3 |
| 2.25 | 16.8 | 21.1 | 21.8 |
| 2.5 | 21.5 | 19.2 | 19.6 |
| 2.75 | 19.1 | 17.6 | 17.6 |
| 3.0 | 18.0 | 16.0 | 15.9 |
| 3.5 | 14.0 | 13.4 | 13.1 |
| 4.0 | 11.82 | 11.3 | 11.0 |
| 4.5 | 9.68 | 9.63 | 9.26 |
| 5.0 | 7.87 | 8.24 | 7.93 |
| 5.5 | 7.05 | 7.12 | 6.87 |
| 6.0 | 6.36 | 6.20 | 6.03 |
| 6.5 | 5.24 | 5.45 | 5.35 |
| 7.0 | 5.07 | 4.83 | 4.80 |
| 7.5 | 3.51 | 4.33 | 4.35 |
| 8.0 | 3.72 | 3.91 | 3.97 |
| 8.5 | 3.63 | 3.56 | 3.64 |
| 9.0 | 3.33 | 3.27 | 3.38 |
| 9.5 | 3.24 | 3.03 | 3.14 |
| 10.0 | 2.86 | 2.82 | 2.93 |
| 10.5 | 2.79 | 2.65 | 2.75 |
| 11.0 | 2.46 | 2.50 | 2.59 |
| 11.5 | 2.35 | 2.37 | 2.44 |
| 12.0 | 2.34 | 2.26 | 2.30 |
| 12.5 | 2.14 | 2.16 | 2.18 |
| 13.0 | 2.03 | 2.07 | 2.06 |
| 13.5 | 2.03 | 1.99 | 1.96 |
| 14.0 | 1.98 | 1.92 | 1.86 |
| 14.5 | 1.87 | 1.86 | 1.76 |
| 15.0 | 1.69 | 1.80 | 1.68 |

the equations of Sapirstein *et al.* (1955). With the additional information from the renogram, unilateral renal blood flows could also be computed.

Because of the contribution from adjacent tissues to renogram counts, the value of $B_{1R}$ and $B_{2R}$ in evaluating unilateral function is a more complicated matter. Some investigators (Block, Hine, and Burrows, 1960) have already found $Y_R$(right)/$Y_R$(left) to be a useful index of differences in function between the two sides. This suggests that $B_{iR}$(right)/$B_{iR}$(left) might also be useful.

As already said, the $F$ test assures us that the best fitting $\gamma_{1i}$'s and $\gamma_{2i}$'s are not identical, as the model requires. There are several possible explanations for this. The rejection is largely due to difficulties with the early part of the blood curve (fig. 2), and thus might be partly explained by difficulties in exact timing, where a very few seconds may make a large difference in the activity of the blood sample in a period. Also to be explored are the possible effects of changing blood flow ($C_{kb}$, $C_{kb}'$ not constant), and changing appearance time. If the model fitted to available data is indeed such a sensitive measure of variations in renal blood flow or urinary appearance time, it may prove to be a valuable tool in studying these variations, and in studying relationships between these two parameters.

## Summary and Conclusions

A model elucidating the relationships between blood radioactivity, the renogram curve, and urine radioactivity, as a function of time, is derived. Estimation procedures have been devised which use the data from three curves at once to estimate parameters common to the three curves, and which also estimate parameters unique to the individual curves. A program has been written for the RPC 4000 computer to perform the estimation.

It was found that some model in which six different exponential parameters could be justified instead of the two proposed by the model could provide a significantly better fit of the data ($P < .001$), but that the fit under the hypothesis was still quite good. It is proposed that the model be retained for further evaluation and study for the following reasons:

1. It is based on soundly established principles of physiology, and hence provides a link between the renogram curve and those principles.

2. The model fits the descending part of the curve well.

3. On the basis of the model we are able to suggest several improvements in the analysis of renograms for clinical evaluation of renal function.

4. The model leads to reasonable estimates of the time of the renogram peak.

5. The model provides a framework for further study of the renogram and its relations to physiologic function in general. More specifically, it may prove to be a sensitive instrument in studying rapid variations in urinary appearance time and renal blood flow, and the relations between blood flow and appearance time.

## References

BERMAN, MONES, EZRA SHAHN, AND MARJORY F. WEISS. The routine fitting of kinetic data to models. *Biophys. J.* 2: 275–287, 1962.

BERMAN, MONES, MARJORY F. WEISS, AND EZRA SHAHN. Some formal approaches to the analysis of kinetic data in terms of linear compartmental systems. *Biophys. J.* 2: 289–316, 1962.

BLAUFOX, M. DONALD, A. L. ORVIS, AND C. A. OWEN, JR. Compartment analysis of the radiorenogram and distribution of Hippuran $I^{131}$ in dogs. *Am. J. Physiol.* 204: 1059–1064, 1963.

BLOCK, J. B., G. J. HINE, AND B. A. BURROWS. Effects of carrier diodrast on excretion of $I^{131}$-labeled diodrast. *J. Lab. Clin. Med.* 56: 110–119, 1960.

GRAYBILL, F. A. Introduction to Linear Statistical Models, Vol. I. New York: McGraw Hill Book Company Inc., 1961.

HOCH, H., AND M. E. TURNER. Studies of rates of escape of proteins through membranes. *Biochim. Biophys. Acta* 38: 410–419, 1960.

KENDALL, M. G., AND A. STUART. The Advanced Theory of Statistics, Vol. I. New York: Hafner Publishing Company, 1958.

SAPIRSTEIN, LEO A., D. G. VIDT, M. J. MANDEL, AND G. HANUSEK. Volumes of distribution and clearances of intravenously injected creatinine in the dog. *Am. J. Physiol.* 181: 330–336, 1955.

STEWART, B. H., AND T. P. HAYNIE. Critical appraisal of the renogram in renal vascular disease. *J. Am. Med. Assoc.* 180: 454–459, 1962.

TAPLIN, GEORGE V., O. M. MEREDITH, H. KADE, AND C. C. WINTER. The radioisotope renogram. An external test for individual kidney function and upper urinary tract patency. *J. Lab. Clin. Med.* 48: 886–901, 1956.

TURNER, M. E., R. J. MONROE, AND L. D. HOMER. Generalized kinetic regression analysis: hypergeometric kinetics. *Biometrics.* 19: 406–428, 1963.

### On Science and Scientists

"I have been developing an ethic for science which derives directly from its own activity. It might have seemed at the outset that this study could lead only to a set of technical rules: to elementary rules for using test tubes, or sophisticated rules for inductive reasoning. But the inquiry turns out quite otherwise. There are, oddly, no technical rules for success in science. There are no rules even for using test tubes which the brilliant experimenter does not flout; and alas, there are no rules at all for making successful general inductions. This is not where the study of scientific practice leads us. Instead, the conditions for the practice of science are found to be of another and an unexpected kind! Independence and originality, dissent and freedom and tolerance: such are the first needs of science; and these are the values which, of itself, it demands and forms."

"Science is not a mechanism but a human progress, and not a set of findings but the search for them. Those who think that science is ethically neutral confuse the findings of science, which are, with the activity of science, which is not. To the layman who is dominated by the fallacy of the comic strips, that science would all be done best by machines, the distinction is puzzling. But human search and research is a learning by steps of which none is final, and the mistakes of one generation are rungs in the ladder, no less than their correction by the next. This is why the values of science turn out to be recognizably the human values: because scientists must be men, must be fallible, and yet as men must be willing and as a society must be organized to correct their errors. William Blake said that 'to be an Error & to be Cast out is a part of God's design.' It is certainly part of the design of science."

J. Bronowski, *Science and Human Values with the Abacus and the Rose.* New York and Evanston: Harper & Row, 1965. pp. 62–64.

# Radiotherapy in the Management of Oral Cancer*

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Radiotherapy and surgery, used singly or in combination, are the only curative approaches to the treatment of mouth cancer. Preoperative irradiation of advanced cancer is now being evaluated, and shows much promise. This may permit operation in previously inoperable cases, make less extensive operative procedures feasible in others, and possibly decrease the incidence of cancer spread during surgery. However, while surgery often can salvage radiation failures, the reverse is seldom true.

## Surgery and Radiotherapy in Oral Cancer

Among surgeons acquainted with the capabilities of good radiotherapy, and radiotherapists familiar with good oral surgery, one seldom finds major differences of opinion about the management of individual cases.

Each method has its advantages and disadvantages. Any acceptable method of treatment must have a good cure rate, a low incidence of complications, and should terminate in the best possible functional and cosmetic result. This last criterion is the least important, but makes radiotherapy of special interest in treating cancer of the mouth. In instances where either method might have equal chances of cure or complication rates, a method that would not interfere significantly with function and appearance is preferable. A normally functioning and normally appearing mouth may not be essential for life, but it is important to the enjoyment of life in our society.

* Presented at a seminar of the department of radiology, division of radiotherapy, Medical College of Virginia, February 18, 1965.

### Cancer of the Lip

Cancer of the lip usually is easily managed by radiotherapy. Its accessibility facilitates the evaluation of the progress of treatment. Shielding adjacent areas from the x-ray beam is easily done, and the results in properly selected and treated cases should be uniformly good. This does not mean that surgery is never indicated. When leukoplakia coexists and can be removed along with the cancer, surgery generally is preferred. The irradiation of lip cancer, be it new or recurrent, near or at the site of previous intensive irradiation, is to be avoided since overlapping these areas invites soft tissue necrosis. The presence of regional lymph node metastasis often will make it desirable to excise these in continuity with the primary lesion. In extensive cases, invasion of the mandible is regarded as a relative contraindication to irradiation since this predisposes to failure and osteonecrosis.

### Cancer of the Buccal Mucosa

In early cancer of the buccal mucosa, surgery and irradiation give about equal cure rates, but radiotherapy generally results in a better functional and cosmetic result. Surgery is preferred for the more advanced fixed ulcerating tumors, particularly those with mandibular involvement or regional node involvement; they are seldom cured by irradiation.

### Cancer of the Tongue

The inaccessibility of carcinoma of the base of the tongue dictates treatment by radiation therapy. The results in squamous cell carcinoma are poor. Metastases to the regional nodes are common, and often bilateral. Irradiation seldom will sterilize these. Furthermore, these lesions generally infiltrate deeply, and control of the primary site is achieved rarely. Occasionally, lymphomas are encountered in this region. Their prognosis is much better because they are considerably more radiosensitive.

Tumors of the lateral margin of the tongue, and the occasional lesion of the dorsum of the tongue, present a more optimistic outlook for the radiotherapist. A significant percentage of these cases can be treated successfully with little functional impairment. Among the lesions to be avoided by the radiotherapist are those with preexistent syphilitic glossitis, those with marked sepsis and edema of the tongue, those which have been previously irradiated, and the extensive lesions with mandibular involvement.

The anterior third of the tongue can be treated by surgery or irradiation. Excision of this portion seldom produces any significant functional impairment, and surgery often is more expedient.

The inability of ionizing radiation conclusively to cope with metastases to regional lymph nodes from squamous cell carcinoma of the oral cavity has already been indicated. Since approximately 80% of patients with cancer of the tongue already have or will develop node metastases (Ackerman and del Regato, 1954), a neck dissection, either prophylactic or for clinically evident disease, usually is a part of the treatment.

### Cancer of the Floor of the Mouth

Cancer of the floor of the mouth responds well to radiotherapy if the mandible is not involved and there is no lymph node metastasis. Even in the presence of node metastases, it often is feasible to irradiate the primary site and do a neck dissection, thus saving the jaw. When cancer of the floor of the mouth involves the mandible, with or without nodes, curative therapy becomes a surgical problem. The same general considerations apply to lesions of both the upper and lower gingiva.

### Malignancy of the Soft and Hard Palates, Salivary Glands, and Tonsils

Lesions of the soft palate should be managed by radiotherapy wherever possible since extensive surgical procedures in this region generally result in considerable disability in swallowing and talking. Lesions of the hard palate are more often handled surgically since surgical defects in this region usually are corrected easily with a proper prosthesis. Adenocarcinomas arising from the minor salivary glands are common in this region and, in general, are not as radiosensitive as the more common squamous cell carcinomas.

Squamous cell carcinoma is the commonest type of malignancy encountered in the tonsil, but lymphosarcoma is not unusual and reticulum cell sarcoma and Hodgkin's disease occasionally are seen here. Irradiation as the primary treatment is usually the choice in each of these instances. The majority of these patients show cervical lymphadenopathy at the time treatment is instituted. While the nodes are included in the field of treatment, radical neck dissection may be necessary following irradiation of the squamous cell carcinoma. The lymphomas, being much more radiosensitive, seldom will need a neck node dissection.

### Problems of Oral Hygiene

When radiotherapy is selected for treating cancers of the oral cavity, the preparation of the mouth for this treatment becomes one of the most important aspects of the therapy. It is often necessary to include the salivary glands in the treatment portals. This causes a temporary suppression of their activity that, depending upon the dose, lasts for varying lengths of time. With the high doses employed in the treatment of squamous cell cancer, the dryness usually persists for several months and the normal flow of saliva seldom is completely regained. A permanent alteration in the chemical and physical characteristics of the saliva occurs. This presumably causes the rapid acceleration of dental caries which is common after irradiation. This type of caries is somewhat peculiar in that the decay occurs at the gingival margin, and the most particular mouth hygiene does not seem to prevent it.

In addition to dental caries, irradiated bone heals poorly and is subject to bacterial invasion. Whenever extraction of teeth from irradiated bone becomes necessary, there is a high risk of a chronic, intractable osteomyelitis of this partially devitalized bone. All radiotherapists do not agree on this point, but most anticipate these possible complications and attempt to avoid them by having extractions done prior to irradiation.

This type of tooth extraction should not be looked upon as routine. Speed is important so that treatment is not delayed. The teeth should be removed in as few sittings as possible. If this is done, with all rough spicules of bone rongeured away carefully, and the gums carefully sutured, normal healing usually results; it is seldom necessary to delay the institution of therapy for more than a few days. When the salivary glands are not to be treated, only diseased teeth and those to be in the beam need be extracted.

### Selection of Radiotherapeutic Procedure

There are many methods of administering radiation therapy to the mouth, and practically every technique has some area of preferred use. Telecobalt and megavoltage are being used in most radiotherapy centers today; however, they have not, and will not, completely replace conventional x-irradiation, radon, and radium.

Conventional orthovoltage x-ray is most useful in accessible lesions, such as the lip or buccal mucosa, and in the occasional small lesion that can be treated with an intraoral cone. As previously mentioned, shielding normal structures from this type of irradiation usually is done easily, while shielding from supervoltage is quite difficult.

Megavoltage irradiation and telecobalt are most useful in the less accessible lesions where it is necessary for the radiation to penetrate bone in order to reach the tumor. Because photoelectric absorption is much less with these modalities, the energy absorbed by the bone is considerably less than it would be from a beam of conventional x-ray; there also is less shielding of the lesions by the bone. A better tumor dose is achieved with a lower given dose, and there also is a significant decrease in skin effect as the maximum ionization occurs subcutaneously.

Radon seeds, interstitial radium implants, and radium molds have the advantage of localizing the radiation to the area treated. Little radiation reaches other sites. This radiation is of a quality comparable to megavoltage and telecobalt, and it has the same bone sparing effect. Radon seeds are used primarily in small tumors which are easily accessible for implantation, such as the buccal mucosa, floor of the mouth, soft palate, or tongue lesions. Interstitial radium needles find their place in the larger, deeper seated tumors of the tongue, floor of the mouth, and buccal mucosa. They are used often with external irradiation. Radium molds can be very useful in areas where they can be made to fit properly, such as the gingiva, hard palate, and floor of the mouth. Some radiation centers treat lip cancers almost routinely by sandwiching the lip between two radium molds. In experienced hands, this gives a very nice cosmetic and functional result. The use of molds by an inexperienced operator is not recommended as they must be properly applied and fitted to do the job well.

A more recent and little-explored radiotherapeutic method of cancer treatment is that of electron beam therapy. The dose from an electron beam is nearly constant to a depth corresponding to the range of these electrons in tissue, which in turn depends upon the accelerating voltage of the machines. With the use of electron beam therapy, the deeper tissues can be spared almost completely from radiation effect, thus reducing complications, discomfort, and the difficulties in maintaining nutrition during and after treatment.

### Complications of Radiation Therapy

The most serious complications of radiation therapy in the treatment of oral cancer are osteonecrosis and osteomyelitis. The advent of megavoltage x-ray and telecobalt has helped greatly to diminish the incidence of these complications, but has not eliminated them. Effective treatment of cancer in any site requires radical treatment, and radiotherapy is no exception. Any method carrying a high incidence of complications is not a good one, but when complications never occur, it usually is at the expense of undertreating.

The dryness of the mouth that occurs when the parotids are irradiated, the aberrations in taste when the tongue is treated, and the membranous reactions of the mucous membranes in the treated areas are troublesome, but should not be looked upon as complications. All possible attempts should be made to minimize these reactions, but usually they cannot be avoided completely.

In a paper given to the American Radium Society, Ash (1962) presented 5-year results on 1,624 patients treated at the Ontario Cancer Institute, representing a 96% follow-up. The crude 5-year survival rates were given in detail by site and stage for cancer of the tongue, buccal mucosa, gingiva, floor of the mouth, and palate. The treatment policy primarily was radiotherapy, with cervical metastasis being managed by radical neck dissections. The overall 5-year results for all sites and stages was 31.5%. These results are typical of what can be expected today with good radiotherapy. Carcinoma of the lip and tonsil were not included in these figures. The tonsil should yield a 30 to 40% 5-year survival, and the lip about 80%.

Whatever definitive form of therapy is used on any given case of oral cancer, one point seems worthy of emphasis. This disease involves many specialities in the field of medicine. For this reason, a team approach to its treatment is desirable. The dentist, the pathologist, the surgeon, and the radiotherapist all have definite contributions to make. Consultation among them prior to the treatment generally will be to the patient's advantage.

### References

ACKERMAN, L. V., AND J. A. DEL REGATO. *Cancer*. 2nd ed. St. Louis: C. V. Mosby Company, 1954.

ASH, C. L. Oral cancer: A twenty-five year study. *Am. J. Roentgenol. Radium Therapy Nucl. Med.* 87: 417–430, 1962.

# Laser in Clinical Ophthalmology: Possible Applications, Limitations, and Hazards

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Since the development of the ruby laser by Maiman in 1959, two major questions have been raised with regard to ophthalmology:

1. What is the feasibility for its clinical use as a therapeutic device?
2. What are the hazards of accidental exposures among personnel working with lasers in industry, research, and military installations; how to counteract them?

After clinical light coagulation for various ocular lesions had been included in the therapeutic armamentarium, the introduction of the laser for similar purposes was obvious, and has been accepted with enthusiasm by various groups of clinical investigators. Since, at present, the ruby laser is only used for ophthalmological purposes, the basic principles of its action are briefly reviewed.

## Fundamentals of Laser Action

When a photon is absorbed by an atom, the energy of the photon is converted to internal energy of the atom. The atom is then raised to an "excited" quantum state. Later it may radiate this energy spontaneously, emitting a photon and reverting to the ground state or to some state in between.

In such an excited state the atom can be stimulated to emit a photon, if it is struck by another photon having precisely the energy of the one that would otherwise be emitted spontaneously. As a result, the incoming photon, or wave, is augmented by the one given up by the excited atom. More important, the wave, upon release, falls precisely in phase with the wave that triggered its release. There must be an excess of excited atoms to enable stimulated emission to predominate over absorption.

In the ruby laser (aluminum oxide poisoned with a few chromium atoms —Maiman used .05% by wt of chromium), light in the green and yellow bands is absorbed, while blue and red are allowed to pass through. The absorbed light raises the chromium atoms to the excited state from which two steps are required to carry them back to the ground state.

First, they give up some of their energy to the crystal lattice and land temporarily in a metastable state. If not subjected to stimulation, their stay at this level lasts a few msec while they drop at random to the ground state.

Photons emitted during this final drop have a wavelength of 6,943 Å (at room temperature). In the laser, however, the first few photons released stimulate the still excited chromium atoms to give up photons and return to the ground state much faster. If a great number of atoms are excited, the ruby merely emits a burst of its typical red fluorescence, spread over the usual decay period for the excited atoms. But above a critical level, in which more than 50% of the total atoms are brought in the excited state, the atoms return to the ground state at the very same moment. They last approximately 200 to 500 $\mu$sec, during which time an intense monochromatic light beam flashes from the laser crystal. The beam is almost parallel if produced at threshold levels. With greater energies increasing divergence occurs.

From the foregoing it becomes obvious that the characteristics of laser radiation are different in several as-

pects from the clinical light coagulator used before. The most important differences are:

1) The spectral distribution of the light source, and

2) The exposure time for production of chorioretinal "burns."

While the conventional Zeiss light coagulator utilizes a xenon high pressure lamp with a spectral range throughout the visible spectrum, the ruby laser beam is monochromatic and produces light at a wavelength of 6,943 Å only. Moreover, the light coagulator allows the ophthalmologist to control the exposure time by pressing a button situated on the ophthalmoscope handle; thus the exposure time is determined under direct vision of the developing tissue response. On the other hand, the exposure time with the use of the laser is inherent within the instrument, and is not controllable during the exposure. Thus, while the light coagulator exposures usually range from about 0.1 sec to 1 sec, ruby laser exposure times are in the neighborhood of 500 $\mu$sec.

These two factors—wavelength and exposure time—however, are of fundamental importance with regard to tissue reaction. During recent years absorption characteristics of the human and the rabbit eye have been studied, especially with respect to absorption distribution in the pigmented layers of the ocular fundus. The data were compared with reflection measurements from the ocular fundus, and with light energies required to produce ophthalmoscopic visible minimal lesions. Moreover, the influence of blood flow on the development of ocular thermal effect has been investigated. More recently, a histological and histochemical comparison of ocular lesions produced with light coagulation with those produced with a ruby laser has been described. In later studies exposure times for light coagulation were 30 msec and 175 $\mu$sec, while laser exposures were achieved with 200 $\mu$sec for "pulsed" and 30 $\mu$sec for "q-switched" laser action (Geeraets *et al.*, 1960, 1962a and b, 1963, and 1965; Ham *et al.*, 1963).

## Clinical Considerations

### *Initial Promise and Present Limitations*

The Zeiss light coagulator has been used for over a decade to treat such ocular lesions as retinal detachment, vascular lesions of the retina and choroid, inflammatory chorioretinal conditions, iris lesions, etc. As soon as the laser was introduced, several of its features seemed more advantageous relative to this conventional light coagulator:

1) The price of the instrument was expected to be considerably lower than that of the Zeiss light coagulator.

2) The instrument promised to be quite light so that it could easily be carried to the patient's bedside, instead of having to bring the patient to the instrument.

3) The very short exposure times were regarded as beneficial, since with these exposure times the patient would not be able to move his eye, thus eliminating the need for retrobulbar anesthesia.

4) The dim red light of the laser beam ($\lambda$ = 6,943 Å) will not produce photophobia, another reason for eliminating anesthesia.

5) The short-time, high-intensity exposures would allow much smaller lesions than those produced by light coagulation.

However, after several years of clinical and laboratory experimentation, these anticipated advantages appear at present not as obvious or as convincing as a number of investigators had initially expected. Moreover, it is quite certain today that the laser has not broadened clinical indications nor has it opened new fields for therapeutic application of high intensity light.

Several instruments utilizing the pulsed ruby laser are now commercially available. With the desire to develop a therapeutic device having as many safeguards as possible against possible overexposures, the price and weight of the instruments have both increased and are still rising; thus the expected advantages outlined above under 1) and 2) seem not to be warranted. It is true, however, that the short exposure time and the dim red light do not necessitate retrobulbar anesthesia of the patient's eye. This minor advantage is contradicted by the dangers of short-time exposures. When the instrument is triggered, the degree and severity of the chorioretinal lesion is decided upon. Even if the surgeon has followed instructions and started with low instrument settings—i.e., low energy output which does not cause any lesions—and has slowly increased the laser beam intensity, the exposures are not without danger. The energy output of the laser varies from shot to shot in a random fashion unless special precautions are taken. Moreover, the energy control settings of the instruments have only a very small range between therapeutically desirable intensities, and those which will produce severe overexposures. With this narrow range, and the possible fluctuations from one exposure to another, the usefulness of the instruments presently available is limited. Beside these inherent limitations, the irregularities in pigment distribution of the ocular fundus add to the potential hazards which might be encountered. Examination of a number of eyes treated elsewhere with lasers, for various etiological reasons, revealed lesions which were too severe and well above optimal therapeutic levels. Many of the lesions showed centrally located retinal holes with small hemorrhages and pigment clumps extending into the vitreous.

There may be an advantage in producing chorioretinal coagulations with very short exposure times when the exposure has to be made in a region where injury to the nerve fiber layer may result in a large scotoma. Here, the short exposure times allow for the coagulation effect to be restricted to the choroid and outer retinal layers, thus sparing the inner layers of the retina and the nerve fibers passing over the lesion. This observation, made in numerous experiments (Geeraets, Burkhart, and Guerry, 1963), can be explained by the absence of tissue damage due to thermal conduction during actual exposure time, if the exposure times are sufficiently short, i.e., in $\mu$sec. The lesions thus produced must be very mild as heat conduction, continuing from the site of coagulation after the exposure has terminated, might be sufficient to cause coagulation of all retinal layers.

The statement that smaller retinal lesions can be produced with a laser is true, but is of little clinical impor-

tance. I have never observed a clinical situation in which a lesion smaller than that producible with the common light coagulator was desired.

*Use in Retinal Tumors*

Retinal tumors have been mentioned as another indication for laser treatment. Here, too, the same rules can be applied that have been established for treatment of tumors with light coagulation. One might even speculate that the more extensive coagulation effect using common light coagulation techniques may be more destructive to tumor cells than the laser beam. But the very restricted indications for coagulation treatment of ocular neoplasm remains the same for both methods.

Experimental data obtained on tumor transplants within the suprachoroidal space have shown some of the restrictions one has to observe in such attempts of treatment (Geeraets, Ghosh, and Guerry, 1962; Chan *et al.*, 1963). In cases of retinal angiomata, the red light of the ruby is reflected to a great extent, thus unnecessarily increasing the incident total light energy applied to the ocular media and other ocular structures.

## Accidental Laser Exposures

With the very powerful devices developed for industrial, military, and research use, accidental exposures of the human retina have presented a true hazard. Not only the direct exposure to the laser beam, but also laser light from any reflecting surface may result in permanent ocular injury. Since light of the ruby laser ($\lambda$ = 6,943 Å) is dim red, and light from the neodymium laser ($\lambda$ = 1,060 Å) is completely outside the visible spectrum, the potential hazard to the eye is greatly enhanced as no immediate discomfort is experienced by the victim. If the ocular lesion is mild and located in the periphery of the retina, the victim may not even be aware of the accident. I have seen such lesions on routine examination where there was no doubt as to the etiology of the lesion. If exposures occur to the fovea or macular area, as in cases where the patient is "fixing" the laser source along the axis of the laser beam or a reflecting spot, the lesion may be of serious consequence, even with mild retinal lesions. And if both eyes are involved, which most likely will happen if the patient is "fixing" on the bright light, the developing macular lesions may produce permanent visual loss.

In case of high-intensity exposures, for instance, as with the giant pulse laser, central as well as peripheral fundus lesions may lead to an explosion-like disruption of the retina and choroid, with massive hemorrhages into the vitreous, resulting in permanent loss of one or both eyes.

These accidental possibilities have necessitated extensive precautions in most installations and laboratories where laser devices are used. Warning signs have been placed in most locations during actual laser operation. Laboratory facilities and equipment have been painted with dark and dull colors to reduce reflection. Special goggles with hardened lenses and color filters have been developed for eye protection. But in spite of these precautions, accidental exposures are not infrequent. Bright flashes of white light produce photophobia and hence constantly bring the danger of exposure to the persons working with these light sources. With the dark red laser beam or the invisible neodymium beam this reminder is absent, possibly explaining the observed negligence by laboratory personnel involved. For legal reasons it has been recommended that any prospective employee to work with, or in the vicinity of, laser devices be given a very thorough eye examination by a qualified ophthalmologist to record all possible existing fundus pathology or anomalies before the person begins work. Routine follow-up examinations should be performed within reasonable periods to insure that no accidental fundus exposures have occurred without the person's knowledge. All reported possible exposures should get immediate medical attention, since laser lesions are more accurately determined the sooner they are examined after exposure. After longer periods of time, scar formation may not be differentiated from other preexisting inflammatory lesions.

According to Tebrock, Young, and Machle (1963), the principles of controlling environmental laser hazards are:

1) Avoidance of the principal beam and its reflections.

2) Proper education of personnel involved.

3) General information given those who might be casually exposed.

4) Use of warning devices to indicate laser is in operation.

5) Policing and clearing of area for long range operation.

6) Use of proper antilaser eye shields on any observer likely to be exposed.

7) Use of count-downs with persons closing eyes or looking away from pulsed, high-power beam.

8) Reporting of all persistent afterimages to medical department.

9) Funduscopic and slit-lamp examination of all people involved in laser operations.

## Conclusions

In spite of the limitations and potential hazards involved in ophthalmic application of laser energy at its present status of development, further clinical investigation is necessary. It should be restricted to a few centers, experienced in this type of work, and aware of the fundamental physical and biological mechanisms involved. In reality, this practice is not always followed, thus increasing the potential danger of the clinical use of lasers. Although some of the available instruments are beautifully designed and engineered, these attributes alone do not justify their therapeutic use. In my opinion, arrangements to make the present existing laser coagulators commercially available to all clinical ophthalmologists are irresponsible, to say the least. Some of the ophthalmologists are misled by erroneous advertisement and receive their instruction from overzealous sales personnel lacking adequate knowledge of the physical principles of laser, or of the biological, optical, and functional characteristics of the eye.

## Summary

The present status of laser application in clinical ophthalmology is discussed. The differences between conventional light coagulator characteristics and those of presently available ruby lasers for clinical use are compared. The limitations and hazards of laser therapy are stressed.

## References

CHAN, G., D. GUERRY, AND W. J. GEERAETS. Light coagulation and intraocular malignant tumors: An experimental study. *Acta Ophthalmol.* Supp. 76: 5–21, 1963.

GEERAETS, W. J., J. BURKHART, AND D. GUERRY. Enzyme activity in the coagulated retina: A means of studying thermal conduction as a function of exposure time. *Acta Ophthalmol.* Supp. 76: 79–93, 1963.

GEERAETS, W. J., M. GHOSH, AND D. GUERRY. The effect of high intensity light on choroidal circulation. *Am. J. Ophthalmol.* 54: 277–283, 1962.

GEERAETS, W. J., W. T. HAM, R. C. WILLIAMS, H. A. MUELLER, J. BURKHART, D. GUERRY, AND J. J. VOS. Laser versus light coagulator: A funduscopic and histologic study of chorioretinal injury as a function of exposure time. *Federation Proc.* 24, Supp. 14: S-48—S-61, 1965.

GEERAETS, W. J., R. C. WILLIAMS, G. CHAN, W. T. HAM, D. GUERRY, AND F. H. SCHMIDT. The loss of light energy in retina and choroid. *Arch. Ophthalmol.* 64: 606–615, 1960.

——. The relative absorption of thermal energy in retina and choroid. *Invest. Ophthalmol.* 1: 340–347, 1962a.

GEERAETS, W. J., R. C. WILLIAMS, M. GHOSH, W. T. HAM, D. GUERRY, F. SCHMIDT, AND R. RUFFIN. Light reflectance from the ocular fundus. *Arch. Ophthalmol.* 69: 612–617, 1963.

GEERAETS, W. J., R. C. WILLIAMS, W. T. HAM, AND D. GUERRY. Rate of blood flow and its effect on chorioretinal burns. *Arch. Ophthalmol.* 68: 58–61, 1962b.

HAM, W. T., R. C. WILLIAMS, W. J. GEERAETS, R. S. RUFFIN, AND H. A. MUELLER. Optical masers (lasers). *Acta Ophthalmol.* Supp. 76: 60–78, 1963.

MAIMAN, T. H. Stimulated optical radiation in ruby. *Nature* 187: 493–494, 1960.

TEBROCK, H. E., W. N. YOUNG, AND W. MACHLE. Laser—Medical and industrial hygiene controls. *J. Occupat. Med.* 5: 564–567, 1963.

# What is a Modern Physician?*

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The first thing to remember is that the patient is not just a pair of tonsils, or perhaps, a skin, a prostate gland, or a pregnant uterus. This is a person. And it is essential that you should treat the patient as a person, as an individual who has feelings just like you and I have, who has a family background like you and I have, who has personal, domestic, and business problems, as most of us have.

Now, the second thing I think we have to take into account is our own problems and our own ignorance. I personally feel that if ever I know anybody who knows more about the subject than I do that I can call him in, if it is necessary. One obviously does not want to bring in a very eminent thoracic surgeon merely because one's patient has an acute bronchitis. But one would always like to feel that if one gets into difficulties, one could.

I learned a great deal by being associated with two Sergeant-Surgeons to Their Majesties. (The office of the Sergeant-Surgeon is a very ancient one, and it his function to accompany the monarch into battle.) The first one that I knew was Wilfred Trotter. He became a fellow of the Royal Society because of his contributions to psychology. He was the man who invented the herd-instinct. Wilfred Trotter was primarily a brain surgeon, but he was an excellent general surgeon. When he was asked to come and see a very difficult patient, the patient always became like clay in Trotter's hands. And I know how he did it. He always listened to what the patient had to say, and he made it plain that he had listened, and not only that, that he had understood. I think this is the first function of any physician, whether he happens to be what you call, I understand, a pill doctor, a cutting doctor, or a talking doctor.

This second thing I learned from Sir Thomas Dunhill, who was Trotter's successor as Sergeant-Surgeon to the King. Dunhill was an Australian, and he started off as an assistant in a pharmacy in Melbourne, and he made enough money to put himself through medical school. He became an expert in thyroid surgery and operated upon the Princess Royal. He was such an extremely safe surgeon that he then was made Sergeant-Surgeon to the Queen. Dunhill would not operate on any of his patients unless I had seen them first. (He ran the surgical service and I ran the medical service together during the war.) He always liked for me to see his patients, in case he had missed something. I remember that he once told one of his patients, who was getting a little impatient, "Mrs. Smith, I'd like you to know that we like to make our mistakes before we operate, and not during the operation, or after." Dunhill was prepared to take an enormous amount of trouble. Queen Mary had some varicose veins. Dunhill did not know what to do about varicose veins, so he went to the Varicose Vein Clinic at St. Bartholomew's. There he watched the interns and residents injecting varicose veins. Then, next week, he went to see what they looked like, and he did some himself. Then, the following week, he went to see what his looked like. When he thought they were all right, he went and did Queen Mary's. So you see, I take the view that a specialist ought to be a physician, basically, and that he should put his specialty on top of being a physician, not instead of it. I frequently find my colleagues in the ear, nose, and throat department are quite unable to take off the patient's shirt. And eye doctors are rather like that, too. And I am afraid sometimes the psychiatrists are a little like this, too. I am not sure that I think this is a good idea. I think one wants to be a general doctor first, and then a special doctor.

Could I pass onto the "machine" side of medicine. I have spent a great deal of my time working in laboratories. One of the things that one learns when one works in laboratories is that things can go wrong. And you sometimes find results which you cannot repeat and you find that the standard reagent has been made up wrong; you find that something has happened so that a record that you were getting is not right. So I have come to regard the laboratory as fallible. And so, as I like to do things myself, and as I can take my own history, and as I can make my own physical examination, and as I can test the patient's urine myself, I tend to place as much or more reliance on the history and the physical examination and the testing of the urine, which are the things I do myself, as I may on the results which come on sheets of paper. The other thing that I like doing a great deal is to add to my own powers of visualization the powers which are added when you make a chap transparent in the x-ray department. I personally very much like to go and see any patient I have screened (fluoroscoped), so that I can actually see with my own eyes what happens when he becomes transparent, and compare that with what I can see when he is opaque. I have said enough about what I think about the problems of tomorrow's physicians, and I hope somebody is going to disagree with me.

*Dr. Pickering:* What do the residents feel is their chief problem, Dr. Thompson?

*Dr. W. T. Thompson, Jr.:* I think that among the very real problems we face here, as we talk with members of

* An informal talk to the medical house staff at the Medical College of Virginia, October 7, 1964.

the department who are in training, are how much training is necessary, and what should the goals of training be in terms of future practice. In other words, what is the place of a general practitioner versus one who is a superspecialist. We have an interesting decision in this school regarding the role of the general practitioner in medical education and also in service to the public. There is no question that he is an essential man in our medical community, and yet we have some difficulty in knowing specifically what his role may be. We tend to think that it varies from place to place. Some of the men here in training in the department of medicine doubtless are going to be general practitioners. Others may be uncertain as to what a family internist is and how much training he needs. I wonder if your staff thinks about their long-range goals in their formative years, and has similar problems about how to make these decisions.

*Dr. Pickering:* I think we have. I think these are very general problems. Regarding the first question, about the length of time that one should take over training, I think this must vary a good deal. On the one hand, the advantage of this period of training is that you can work under a lot of people who will tell you a great deal. Your responsibilities, in a way, are rather limited to the kind of responsibilities that you get in a hospital. On the other hand, there is your desire to be an independent person, so to speak, and the fact that, in a way, your training is going to be for the rest of your life. I have learned, I think, really more since I became a responsible person than I did when, so to speak, I was responsible to someone else. So I think everybody probably will have to decide to choose between these two kinds of considerations.

You know, there was a time when James MacKenzie, who was a general practitioner and a physician and surgeon to the Royal Victoria Hospital in Barkley, made a lot of his important observations when he was operating on the abdomen of patients without any anesthesia. Well, our general practitioners do not operate on the abdomen now. A lot of them used to make considerable income by taking out tonsils and adenoids. They don't take out tonsils anymore. I think the general practitioner is terrified of treating fractures because it is not true that the bones are full of red and yellow marrow; they are full of black ingratitude. Unfortunately, they have a horrible habit of producing large amounts in damages and therefore practitioners are a little bit wary of them. They tend to always get sent to the orthopedic surgeon now. So, with us, the general practitioner has almost become a family physician. I think we increasingly feel that the general practitioner should have some training in surgery, and, of course, ear, nose, and throats are very important because they are so common in country practice, and skins are important because they are very common, and pediatrics is important because there are lots of children, and psychiatry should be important because many of the problems have to do with the mind. Yet the main training ought to be in internal medicine because it has to do with the whole lot, really. And it has to do with the patient as a whole. I think the important thing about the general practitioner is that he is better at deciding if he needs specialist help, and, if so, what specialist to call in, than the patient is himself. I think this is one of his major functions. Whether another general practitioner should take part in his training, I do not have any very strong views. Our general practitioners feel they should. But, I think they inevitably take part in the training of the family physicians afterward, because he joins a group of them and they train each other.

*Question:* Would you tell us some differences between postgraduate education in Great Britain and here?

*Dr. Pickering:* Yes. In Great Britain it is less organized than it is here, and there the postgraduates have to pick up what they can. Here they have a great deal provided for them in the way of seminars, conferences, and lectures. I think it is better organized in the United States than in Great Britain. We are trying to organize it and I hope we are going to get better.

*Question:* Has socialized medicine affected the number of people going into specialization?

*Dr. Pickering:* Yes. It has increased them. At least, I would think it has increased them. By the way, why do you call it "socialized medicine?" It is very interesting. What we say is that we have got a National Health Service, but I always get asked a question of this sort about "socialized medicine." Really, the war started all this. You know, I often tell people that the architect of the National Health Service is a chap called Adolph Hitler, because we developed the National Health Service during the war. It was called the Emergency Medical Service, and it simply continued into the National Health Service. What happened was that, during the war, the big London teaching hospitals and the big city hospitals were evacuated because of the fear of bombing. Lots of country places were upgraded, including the old workhouse infirmaries, and they got staffs of decent physicians and surgeons attached to them. It has been a policy of the National Health Service to see that a place like, say, Cornwall—which you know is way down in the southwest tip—that this is served by a pediatrician, an obstetrician, a physician, and a surgeon, so that disease was covered. Before they went there, because the community was not rich enough to support these people by private practice, the local inhabitants were rather badly served, except for those who were rich enough to go to London or one of the other big cities. So my answer is that the National Health Service has increased the number of specialists. The main complaint with the Service, and this is very justifiable, is that the general practitioners have a little more paper work in that they have a lot of certificates to sign. But they do not have to send out bills. They are largely cut off from hospital practice, and they have not done as well financially as the consultants. I think the main problem in our National Health Service now is to make family practice sufficiently attractive to draw good people into it. There is a working party at the moment trying to achieve this.

*Question:* That's one of the big problems we face, and how do you go about making it attractive?

*Dr. Pickering:* I think there ought to be a lot more ancillary help. I would have thought it would be desirable for family practitioners to prac-

tice from health centers in which they had secretarial help, record keeping, a nurse or two, a laboratory, some x-ray equipment, and that they would arrange their time so that they worked something like an 8-hour day, instead of being on call the whole time.

*Question:* The problem here is not the ancillary help, which most of the practitioners can afford to hire. The 8-hour day is one of the problems. But, I think another real problem is that practitioners feel cut off in many cases; they are so busy with their practice that they don't have time to keep up, and they get farther and farther behind. That is why so many of them come back for house-staff training after some years of training.

*Dr. Pickering:* Well, we have the same problem, only more so.

*Question:* We had a general practice internship setup here. The usual procedure was to stay in it one year and then go into some specialty. Another thing about the local doctor—and he may have got himself into it—is that he has made himself a middle man. He feels he is just shifting or directing patients to specialists, and feels quite limited in scope and power.

*Dr. Pickering:* Our best ones are very powerful with their patients. They won't allow a surgeon to operate if they do not think he is right. And I think this is a good thing. We have some extremely competent general practitioners around about Oxford, and they are terribly useful because they save their patients from all kinds of things that are not in their patients' interest to have done.

*Question:* Our patients seem to get their direction from the *Readers' Digest*. Actually, I believe our patients are a little harder to manage. They come up with ideas of their own. They ask the bus driver what he would do, read the *Readers' Digest* or *Time*, and then come up with pretty firm ideas about where they are going and who they are going to see.

*Dr. Pickering:* One of the important functions of my general practitioner is to protect me from the orthopedic surgeons, whose teeth water every time they see me.

*Question:* Can your patients get to a consultant without going through a general practitioner?

*Dr. Pickering:* Difficult. Most consultants will not accept a patient unless he is sent by a general practitioner. It can be done, but it is not easy.

*Question:* I wonder how often your general practitioner's hand is guided or forced when a patient comes to them with some idea of who he wants to see. This to me seems to leave no defensive position at all.

*Dr. Pickering:* He has got to do that. If the patient says, "I want to see someone," he has to send him there.

*Question:* One of the objections to the National Health Service is that there are so many unnecessary calls on the physicians. What do you think can be done?

*Dr. Pickering:* I don't think anything can be done. There always have been a lot of unnecessary calls. There always have been patients who abuse their doctors. I remember vividly meeting a Canadian doctor who told me that his father was a general practitioner in the country in Ontario. When he was about 12, his father got a night call in the winter. Because there was a lot of snow on the ground, the old doctor took his son with him. They had to dig themselves out of one or two snowdrifts. When they got to the farmhouse, the baby was born, and the grandmother upbraided the doctor for being late. As they were going away, the boy said to his father, "Dad, why did you stand for that sort of thing?" And the doctor said, "Well, son, you know, this is just one of those things. This is the sixth child I have delivered for them, and they haven't yet paid me for the first one."

*Question:* Does the general practitioner, by being denied the privilege of seeing the hospital patients, have his perspective seriously narrowed? Can he stay "modern" without hospital experience?

*Dr. Pickering:* Well, I think that depends how the local hospital caters to him, what advantage he takes of it, and how he reads. But I see your point. On the other hand, it has protected the patient a great deal because we do not now have incompetent surgeons trying to remove breasts and that sort of thing.

*Question:* Has there been any change in the quantity or quality of young men who aspire to be doctors in Great Britain?

*Dr. Pickering:* It is generally supposed that the quality has fallen off, but the quantity is terrific. We still only take about one applicant in six or seven, but I am constantly being pestered by schoolmasters and parents who cannot get their boys into medical schools. I think the falling off in the quality of the students reading medicine is a general phenomenon. I know it is happening at several schools in this country. I think it is because there are many attractive alternatives, such as space research, agriculture, physics, and even business.

*Question:* Is there any truth in the claim that this country is draining England's medical brains?

*Dr. Pickering:* Oh yes. But you've been doing this now for about 300 years.

# Central Nervous Control of Blood Pressure in Man; Preliminary Report*

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Clinicians have long recognized the importance of the mind in the moment-to-moment regulation of blood pressure in their hypertensive patients. Ayman and Goldshine (1940) long ago demonstrated that blood pressure measured by a physician in a hospital clinic was always higher than the pressure recorded by the same patient or by a member of his family in his home. Pickering's group (Richardson *et al.*, 1964), using an automatic blood pressure recorder, has recently shown that elevation in blood pressure ranging from 10 to 50 mm Hg occurred when a physician entered the patient's room merely to say a word of greeting. Figure 1 illustrates the dramatic rise in the pressure of a hypertensive subject during examination by an unfamiliar neurologist who concluded, within the patient's hearing, that brain damage was present.

To study further the relation between cerebral activity and blood pressure, we have recorded electroencephalograms and intra-arterial blood pressure in normal people during natural sleep.

## Materials and Methods

The subjects of these experiments were twenty-two healthy volunteers, five women and 17 men, aged 19 to 51 years, two hypertensive patients recently recovered from heart failure, and one totally-nephrectomized man awaiting renal transplantation. Blood pressure and heart rate were recorded continuously through a soft plastic catheter inserted into a brachial or radial artery. Cerebral electrical waves and eye movements were recorded with a Grass electroencephalograph from electrodes pasted on the scalp and beside the eyes. Rate and depth of breathing were recorded with pneumographs placed around chest and abdomen. The subjects slept on their backs in a bed in a dark, quiet room. Recording equipment and observers were in an adjoining room. No sedatives were given.

The depth of sleep was assessed from the electroencephalogram by the scheme of Oswald (1962). Dreaming was recognized by the occurrence of rapid conjugate eye movements during light (stage B) sleep, as first pointed out by Dement and Kleitman (1957), who observed that subjects awakened just after a burst of rapid eye movements described dreams vividly. On the other hand, if they were allowed to sleep for 5 to 10 minutes after the eye movements stopped, and were then awakened, their recall of dreams was diminished or lacking. These eye movements signal the presence of

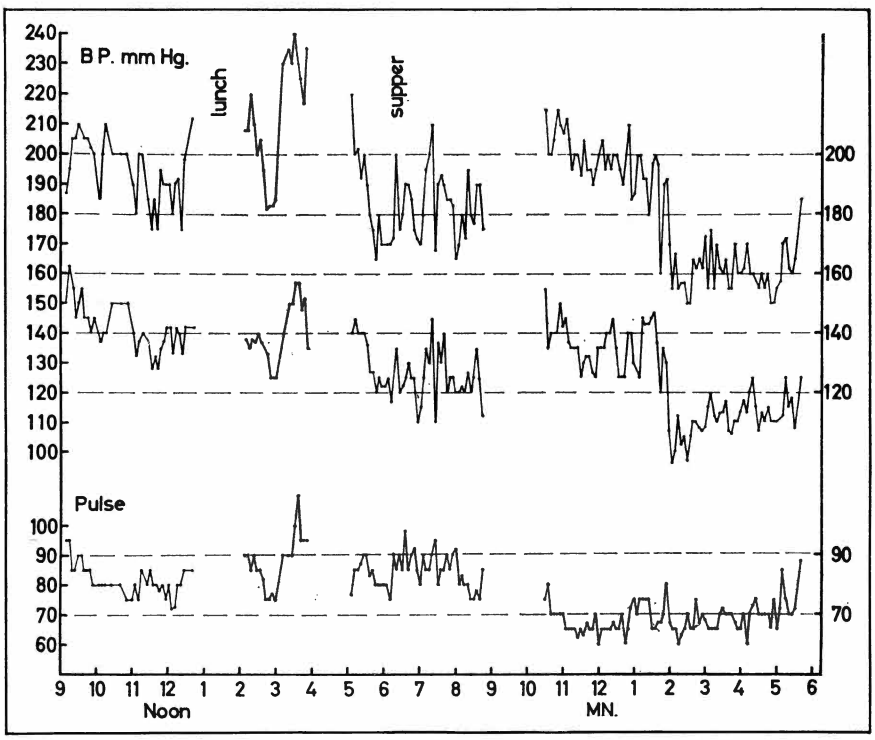


Fig. 1—Arterial pressure and pulse rate recorded indirectly at 5-minute intervals for 24 hours in a young, hypertensive man. At 2:40 p.m. he was awakened from a nap by a consultant neurologist. At about 1 a.m. he fell asleep. Reproduced by permission of the editors of *Clin. Sci.* (Richardson *et al.*, 1964). Variation in arterial pressure throughout the day and night.

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dreaming but provide no information about the content of the dream.

In three subjects, the changes in blood pressure which follow the type of paroxysmal cerebral electric activity called K complexes (fig. 3) were observed before and during blockade of $\beta$-adrenergic receptors with 5 mg of propranolol given intravenously without waking the subject (Courtesy of Dr. Alex Sahagian-Edwards of Ayerst Laboratories, 685 3rd Ave., N.Y. 17, N.Y.). Blockade of $\beta$-adrenergic receptors prevents the increase in cardiac output and heart rate induced by stimulation of sympathetic nerves, without preventing the peripheral arterial constriction which sympathetic neural discharge produces. The use of propranolol thus can yield information about the mechanism by which cerebral activity produces a rise in blood pressure. The effectiveness of $\beta$ blockade was tested in each subject by intravenous infusion of 10 $\mu$g of epinephrine per min. This produced marked elevation of blood pressure and slowing of the heart when given after propranolol, instead of the usual response of tachycardia without change in mean blood pressure.

## Results

### *1. Effect of Sleep*

In four healthy subjects, systolic pressure fell more than 60 mm Hg between the highest waking pressure and the lowest sleeping pressure; in ten, systolic pressure fell more than 50 mm Hg. The average fall in systolic pressure for nineteen normal subjects was 49 mm Hg. Diastolic pressure fell less than systolic, with an average change from waking to sleeping of 29 mm Hg. About 40% of the total decrease in pressure occurred while the patient was resting prior to onset of sleep; the remaining 60% occurred after sleep began. Prompt rise in pressure occurred as soon as the subjects awoke in the morning, and during brief periods of wakefulness during the night. Subjects whose waking pressure was highest experienced the largest decreases in pressure during sleep. No clear correlation was observed between depth of sleep, judged by the electroencephalographic criteria, and level of blood pressure.

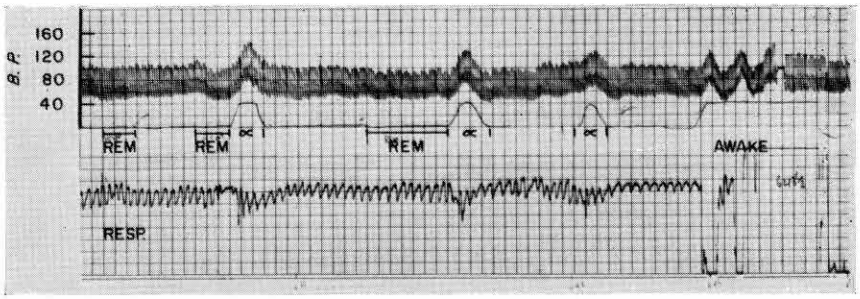


Fig. 2—Intra-arterial pressure (upper tracing) recorded continuously during the end of sleep in a healthy young man. The periods marked REM indicate rapid eye movements associated with dreaming. During the periods marked "$\alpha$" there was brief arousal. Each vertical line represents 5 seconds. The entire graph represents 5½ minutes. See text.

### *2. Dreams*

Figure 2 shows a typical example of the variable changes in blood pressure that occurred during periods of rapid eye movements which indicate dreams. The bars marked REM indicate the bursts of rapid eye movements. The periods marked "$\alpha$" indicate brief wakefulness following each dream. The first dream did not alter blood pressure. During the 2nd and 3rd dream periods, blood pressure fell slightly. In other subjects, a rise of pressure as much as 45/30 mm Hg that reached levels of 180/100 mm Hg, occurred during the periods of rapid eye movement. Each subject showed considerable variability in the response of arterial tension to dreams, perhaps related to varying content of the dreams.

### *3. K Complexes*

During sleep of moderate depth, there occur paroxysmal bursts of cerebral electrical activity called K complexes, which are characterized by one or more large (50 to 200 $\mu$v), slow (0.5 to 1 cycle per sec) waves on which are super-imposed regular, higher frequency (about 14 cycle per sec) waves called sleep spindles. The large, slow waves are recorded all over the head; the spindles are maximal in the frontal regions. The anatomic site of origin of K complexes, and their functional significance, are unknown. K complexes frequently follow within a few msec a noise or a light flash, but may occur without obvious external stimuli. Many of these K complexes are followed by a rise in blood pressure, as shown in figure 3. Heart rate speeds slightly as the pressure rises following a K complex, and slows below the resting rate at the height of the rise. The rise in arterial pressure begins two or three heart beats after the onset of the K, and lasts 10 to 20 seconds. In six healthy subjects whose records have been completely analyzed, K complexes were associated with an average rise in systolic pressure of 18 mm Hg, with maximal rises of 35 mm Hg in two subjects.

### *4. Blockade of $\beta$-Adrenergic Receptors*

In three healthy subjects, effective blockade of $\beta$-adrenergic receptors, as indicated by reversal of the usual effects of intravenously administered epinephrine, did not modify the pressor response to K complexes. Figure 4 shows the rise in pressure occurring with a K complex after the injection of propranolol, the $\beta$-blocking drug, into the same subject shown in figure 3 prior to injection of propranolol.

## Discussion

### *1. Circulatory Effects of Sleep*

Sleep reduces blood pressure in normal and in hypertensive people (Richardson *et al.*, 1964). The neuroanatomic basis for this circulatory change is unknown in man, but ablation experiments in animals indicate that connections between the reticular formation in the midbrain and the cerebral cortex are necessary for wake-

fulness (Oswald, 1962). A current hypothesis suggests that activation of the cerebral cortex by ascending impulses from the mesencephalic, reticular, activating system produces wakefulness, and that impulses from the same area result in sympathetic discharge to the heart and blood vessels, either indirectly by activation of higher brain centers, or more directly by descending fibers to the medullary circulatory centers.

Clinical application of sleep as therapy for high blood pressure has been used by Russian workers who have induced prolonged sleep pharmacologically in the management of hypertension. The long-term efficacy of such therapy is not well evaluated.

### 2. *Dreams*

Snyder *et al.* (1964), using indirect (cuff sphygmomanometric) and discontinuous measurement of blood pressure have concluded that the blood pressure of twelve subjects in 30 nights of sleep averaged slightly higher during the rapid-eye-movement periods, which indicate dreaming, than at other times. This is a conclusion not borne out by our continuous blood pressure records. The same authors also found that blood pressure and heart rate vary more during dream periods, an observation which our data support. The dramatic rise in pressure occasionally seen with dreaming has obvious clinical import regarding nocturnal angina and paroxysmal nocturnal dyspnea.

### 3. *K Complexes*

The short interval between the onset of K complexes and the subsequent rise in blood pressure (two or three heart beats) suggests strongly that neural pathways are used exclusively to transmit the message from brain to circulation; it is unlikely that adrenal medullary (or other) hormones could be released into the circulation and reach the effector area in so brief a period. Observation of similar hypertensive responses to K complexes in a totally nephrectomized patient demonstrates that the kidneys are unnecessary for this kind of elevation in blood pressure.

Since propranolol, which blocks the

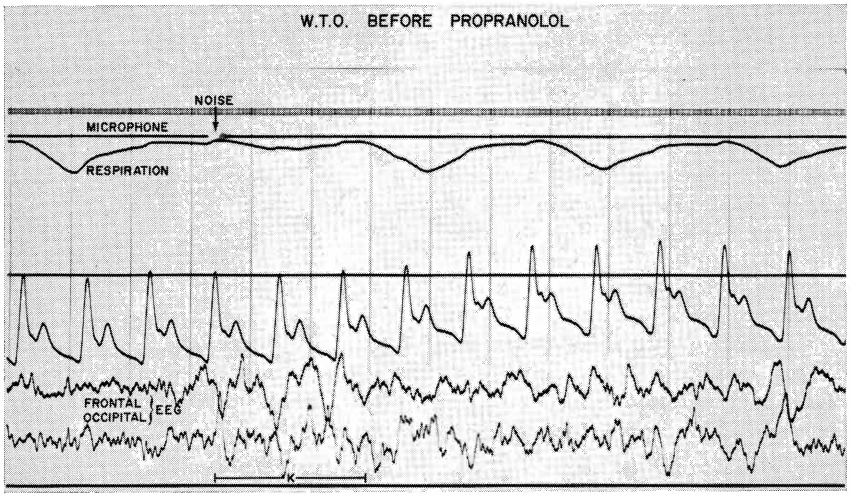


Fig. 3—Respiration, intra-arterial pressure and frontal and occipital electroencephalograms from a healthy man during sleep of moderate depth. Each vertical line represents 1 second. See text.

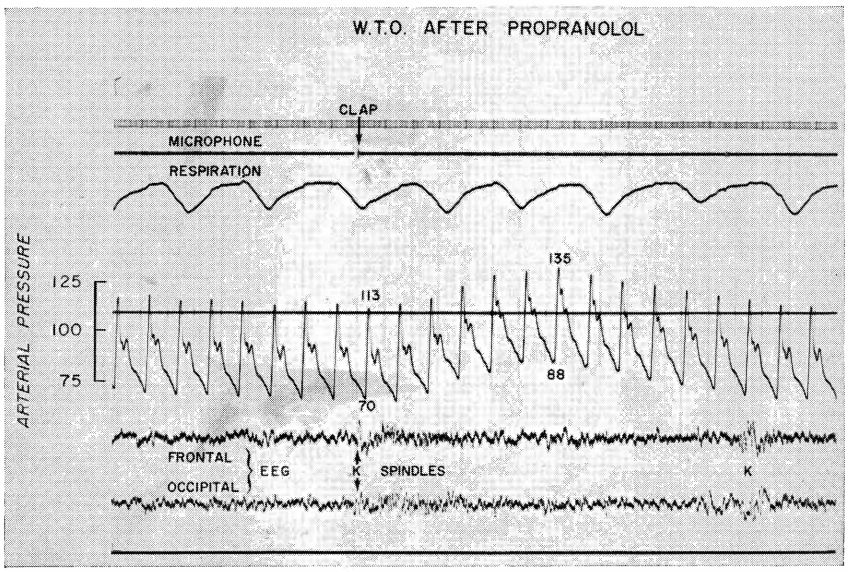


Fig. 4—Response of blood pressure to K complex during $\beta$-adrenergic blockade. See text.

cardiac excitatory effects of sympathetic nerve discharge, did not modify the hypertensive response to K complexes, we presume that the K complexes stimulate sympathetic vasoconstrictor nerves to peripheral arterioles, causing an increase in peripheral vascular resistance, and consequent elevation in blood pressure. The hypertension associated with K complexes clearly demonstrates the importance in man of cerebral activity in moment-to-moment control of blood pressure. The immediate relation between cerebral activity and elevation of blood pressure increases interest in the role of the brain in chronic (essential) hypertension, and as a contributing factor in the abnormal physiology leading to paroxysmal nocturnal dyspnea and nocturnal angina.

## Summary

1. Electrical activity of the brain, eye movements, arterial pressure, heart rate, and respiratory rate and depth have been recorded continuously during a night of sleep not induced by drugs in 22 healthy subjects, two hypertensive patients, and one anephric man who was awaiting renal transplantation.

2. Sleep was associated with reduction in arterial pressure averaging 50 mm Hg systolic and 30 mm Hg diastolic.

3. Dreams, although occasionally associated with marked elevation of blood pressure, were usually accompanied by no change or a slight fall in pressure.

4. The dramatic paroxysmal electroencephalographic alterations termed K complexes, occurring spontaneously or after a noise in sleep of moderate depth, were followed within two or three heart beats by abrupt elevation in arterial pressure, as much as 35 mm Hg, lasting 10 to 20 seconds. Blockade with propranolol of $\beta$-adrenergic receptors, which mediate cardio-excitatory effects of sympathetic nerve discharge, did not modify the hypertension following K complexes.

5. Cerebral activity, transmitted by sympathetic peripheral vasoconstrictor pathways, is an important regulator of blood pressure during sleep in man.

## References

AYMAN, D., AND A. D. GOLDSHINE. Blood pressure determinations by patients with essential hypertension. I. The difference between clinic and home readings before treatment. *Am. J. Med. Sci.* 200: 465–474, 1940.

DEMENT, W., AND N. KLEITMAN. The relation of eye movements during sleep to dream activity; an objective method for the study of dreaming. *J. Exp. Psychol.* 53: 339–346, 1957.

OSWALD, I. *Sleeping and Waking.* Amsterdam, N. Y.: Elsevier Publishing Co., 1962, p. 35.

RICHARDSON, D. W., A. J. HONOUR, G. W. FENTON, F. H. STOTT, AND G. W. PICKERING. Variation in arterial pressure throughout the day and night. *Clin. Sci.* 26: 445–460, 1964.

SNYDER, F., J. A. HOBSON, D. F. MORRISON, AND F. GOLDFRANK. Changes in respiration, heart rate and systolic blood pressure in human sleep. *J. Appl. Physiol.* 19: 417–422, 1964.

# Treatment of Hypertension*

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Our ideas about the management of hypertension have changed considerably in recent years. There is now general agreement that all patients with accelerated hypertension, as manifested by high diastolic pressure and Group III and IV funduscopic changes, should have their blood pressure reduced with antihypertensive agents. Differences of opinion still exist, however, in respect to the treatment of the less rapidly advancing types of hypertension. It is apparent that the life history of untreated essential hypertension varies widely from those patients whose lives are cut short in a matter of a few years, to those who survive to old age. The problem is further complicated because antihypertensive treatment is neither simple, innocuous, or inexpensive.

If we are to approach a solution to this problem we need to know the answers to two questions. The first is: *Does antihypertensive treatment prevent the organic complications associated with hypertension?* and the second, *How can we recognize and differentiate the patient who will develop serious complications from the patient who will live out a normal span of life?*

## Is Therapy of Hypertension Necessary?

Let us consider first the question of blood pressure reduction in preventing organic complications. The evidence is very good that any form of treatment which lowers blood pressure has a beneficial effect on hypertensive congestive heart failure. Cardiac failure has fallen from a major cause of death to a minor cause in adequately treated hypertensive patients. In addition, since antihypertensive treatment is effective in reversing the accelerated phase of hypertension, it follows that the transition to the accelerated phase should be prevented in adequately treated patients. There also is evidence that the incidence of cerebral hemorrhage has been reduced. Thus, it appears that antihypertensive therapy is useful in preventing congestive heart failure, accelerated hypertension, and cerebral hemorrhage.

There are as yet no reliable data to indicate whether antihypertensive treatment prevents atherosclerotic complications such as myocardial infarction and cerebral thrombosis. It is apparent that hypertension accelerates and aggravates the atherosclerotic process. Hypertension in some way predisposes the arterial walls to the deposition of atherosclerotic plaques. Atherosclerosis is commonly found in the pulmonary artery, for example, in long-standing pulmonary hypertension, and in the aorta in the region of high pressure above a coarctation. Once formed, however, it seems highly unlikely that atherosclerotic plaques could be influenced by antihypertensive treatment. In addition, we know that chronic elevation of pressure leads to structural changes in the arterial walls, including fragmentation of elastic tissue. It is possible that these irreversible structural changes provide a favorable environment for the development of atherosclerosis even after the blood pressure has been reduced. These considerations suggest that blood pressure must be lowered in the early stages of hypertension if antihypertensive treatment is to favorably influence the future course of atherosclerotic complications.

We have similar evidence that hypertension leads to the structural changes in the renal arterioles that we call nephrosclerosis. The rapidity of development, and the severity of the nephrosclerotic process, appears to depend on both a persistently high diastolic pressure and a susceptible individual. In the presence of renovascular hypertension, where a stenosis of one renal artery is present, producing a pressure drop across the narrowed segment, nephrosclerosis develops in the opposite kidney whose arterioles are exposed to the high systemic pressure. In the kidney with the pressure drop, whose arterioles are exposed to a more normal pressure, nephrosclerosis is minimal or nonexistent. If nephrosclerosis is to be prevented, this again suggests that elevated blood pressure must be lowered at a relatively early stage in the disease.

If there is a relationship between elevation of blood pressure and atherosclerosis, as well as nephrosclerosis, then it is reasonable to assume that the extent of these pathological changes will depend on both the height and the duration of the blood pressure. If the blood pressure is high for only brief periods of time, and is normal at all other times, we would *not* expect to find vascular pathology. However, if the pressure is high all of the time, both day and night, and if this persistently high pressure lasts for many months or years, then vascular pathology would be expected.

## Variability of Blood Pressure Readings

Blood pressure represents a variable manifestation. It can be strongly influenced by emotion, particularly by fear and apprehension. There are some individuals who from childhood manifest transient elevations of blood pressure, associated with apprehension, who never develop a persistent eleva-

* Presented at the Thirty-sixth Annual McGuire Lecture Series at the Medical College of Virginia, October 8, 1964.

tion of blood pressure throughout a normal life span. These individuals may, in middle and older age, exhibit pressures of 230/130 or even higher during a visit to a doctor's office or a clinic, and yet at home their blood pressure will be normal. Such hyperresponsiveness may develop in middle age, particularly in females, or in old age in both sexes, as was shown by Pickering almost 30 years ago. These individuals may show very little organic progression.

Other hypertensive patients exhibit elevation of blood pressure throughout the day, whether they are at home or hospitalized. These patients will almost all exhibit organic changes, and the rate of progression varies in general with the height of the diastolic blood pressure.

### Predicting the Prognosis of Hypertension and Need for Therapy

Thus, in evaluating hypertensive patients for treatment, we should consider not only the height of the blood pressure but, more important, its persistence or duration. When we measure blood pressure only in the office or clinic we should realize that we are being presented with a mixture of populations, some of which have severe pressure elevations most of the time, some with considerably less hypertension than they exhibit in the office most of the time, and some which are not hypertensive at all but hyperreact to situations associated with apprehension.

Another way of estimating prognosis is to determine whether organic changes are already present. We should utilize the history, the funduscopic examination, the electrocardiogram, chest x-ray, and renal function tests to estimate the degree of such damage. Unfortunately, these changes do not become apparent by ordinary clinical tests until structural damage is already well advanced. As pointed out previously, if antihypertensive treatment can be expected to produce a beneficial effect in preventing nephrosclerosis and accelerated atherosclerosis, it should be given in an early stage of the disease.

It seems evident, therefore, that physicians should obtain a more accurate estimate of the average blood pressure than has been customary in the past. If the office blood pressure is not a reliable guide, then we should determine what the blood pressure is under more representative circumstances. The most representative blood pressure that is practicably obtainable is that recorded in the home, not by the physician but by the patient himself, or better yet, by a member of his family. The office nurse can easily and quickly teach such individuals how to record blood pressure, and a few manometers can be kept on hand for two-week loans. The pressure should be recorded morning and evening for two weeks in the home and the record brought to the office on the next scheduled visit. Frequently, the blood pressure readings drop immediately or over a period of days to normotensive levels. However, *the finding of a persistent diastolic elevation above 90 mm of Hg is an important criterion for instituting antihypertensive treatment.* The higher the elevation, the more intensive the treatment will be. Of course, it is important to make certain that the blood pressure is being taken accurately by having the individual record the pressure in the physician's presence at the time of the office visit.

Other useful prognostic indices, besides the estimate of the average blood pressure and the survey for organic damage, are the age, sex, and race of the patient, and the rate of progression. These factors are well known and require no emphasis.

### Antihypertensive Drugs

#### *Saluretic Agents (Thiazides); Reserpine and Hydralazine*

In the patient with persistently elevated diastolic blood pressure, but with little or no signs of organic damage, treatment can begin with an oral saluretic agent. This generally is not sufficient by itself to reduce the diastolic pressure to normal. If it is not, 0.5 mg of reserpine twice daily for two weeks, followed by a maintenance dose of 0.25 mg once daily can be added; or else hydralazine (Apresoline) may be added in a dose of 25 mg two to three times daily. If the latter is not effective, the dose can be increased gradually to 50 mg three times daily.

Saluretic agents plus reserpine frequently provide an effective combination therapy in uncomplicated hypertension. The regimen also is convenient because long-acting diuretics can be combined with 0.25 mg of reserpine, to be taken only once daily.

The principal toxic effect of reserpine is mental depression. Generally, the more intelligent the patient, the greater the danger of reserpine-induced depression. Unfortunately, other alkaloids of Rauwolfia are not very effective as antihypertensive agents and, therefore, cannot be substituted. It is important when prescribing reserpine to tell the patient that if he should begin to feel unaccountably depressed or to develop sleep disturbances, such as early morning awakening, he should immediately discontinue the drug. In addition, one should strive for the lowest possible maintenance dose, which lies between 0.1 mg and 0.25 mg daily in different patients.

The serious toxicity associated with hydralazine is definitely dose dependent. The chief toxic reaction consists of a syndrome resembling disseminated lupus which rarely, if ever, occurs when the total daily dose is maintained at 150 mg or less per day. The acute side effects of hydralazine can be avoided by a few simple maneuvers. The first is to add hydralazine to the regimen of a patient already being treated with a diuretic or reserpine or both. The latter two drugs, and particularly reserpine, tend to combat or neutralize the acute hydralazine side effects which are headache, palpitation, and tachycardia. The second maneuver is to institute the drug in low and widely spaced doses, increasing gradually. For example, hydralazine can be started in a dose of 25 mg once daily, increasing in two or three days to twice daily, and after a similar interval to three times daily. It is surprising how frequently a small dose of 25 mg two or three times daily is effective in uncomplicated hypertension when it is added to the diuretics with reserpine, or to reserpine alone. The trial of hydralazine, however, should not be abandoned until the dose has

been increased to 50 mg three times daily.

*Drugs in combination*

The results of the large scale double-blind V.A. Cooperative Study on Antihypertensive Agents clearly showed the additive effects of these three drugs in producing a reduction of blood pressure. The combinations of reserpine and thiazides, or of hydralazine-reserpine, or hydralazine-thiazide were clearly more effective in reducing blood pressure than any of these agents used alone. The combination of all three agents was most effective, reducing the average diastolic blood pressure to below 90 mm in the patients that had been classified as having hypertension of mild and moderate severity.

In patients whose blood pressures are not controlled with any of these combinations of diuretic-reserpine and hydralazine, it is advisable first of all to make certain that you are not being misled by high office recordings. Patients whose blood pressures are well controlled at home may completely overcome the antihypertensive effects of the drugs in the office or clinic. Here again a record of home blood pressures, taken over a two week period, will go far to clarify the situation.

Since the saluretic agents are used so widely in the treatment of hypertension, it is important to consider their adverse reactions. The most common disturbance produced by thiazides is a reduction in serum potassium levels. This usually causes no difficulty unless the patient is receiving digitalis alkaloids, in which case arrhythmias frequently are induced, due to the increased activity of digitalis in the presence of a reduction in extracellular potassium concentration. Although it is customary to advise ingestion of excess potassium in this circumstance, this cannot be depended upon to raise the serum potassium level.

Another frequent side effect of thiazide administration is hyperuricemia due to inhibition of renal tubular secretion of uric acid. In azotemic patients, this frequently precipitates attacks of gout. It seldom does in non-azotemic patients. It is advisable to control the blood pressure without thiazides in patients who develop gout. However, at times the situation demands thiazide treatment. In such a case probenecid is given to combat the hyperuricemia and colchicine is administered when necessary to control symptoms.

Patients with severe renal damage and acidosis often are unable to conserve salt. If they are placed on salt restricted diets, and at the same time are given thiazides, nitrogen retention may be intensified. The administration of sodium bicarbonate or sodium lactate to such patients sometimes results in diuresis with a fall in BUN and in the degree of acidosis.

Diabetes mellitus is occasionally precipitated by thiazides. The incidence of this complication is low and it is difficult always to distinguish between spontaneous diabetes and the drug induced variety. Finally, thiazides may induce hypersensitivity reactions with skin rash and, on rare occasions, thrombocytopenic purpura.

*Adrenergic Blocking Agents*

If the response to a combination of diuretic plus low doses of reserpine and hydralazine truly does not control the blood pressure, the physician has the choice of using diuretics plus adrenergic blocking agents, such as methyldopa (Aldomet), guanethidine (Ismelin), or pargyline (Eutonyl).

Orthostatic hypotension poses the main problem in administering the adrenergic blocking agents. The physician should be prepared to deal with this side effect if he is to effectively treat patients with severe hypertension. The important points in managing patients undergoing treatment with the blocking drugs are these:

1) Use saluretic agents in conjunction with blocking drugs whenever possible. The former tend to smooth out the large diurnal fluctuations of blood pressure induced by the blocking agents, and to maintain a more constant antihypertensive response from one day to the next. Saluretic agents also increase the responsiveness of the blocking agents, permitting lower doses of the latter.

2) Tell the patient at the time treatment is begun that the drug lowers the blood pressure in the erect position, that it may reduce it to such a point that he feels faint, but that the dose can be adjusted so that this symptom will not be troublesome.

3) Tell the patient that, if he does develop weakness or faintness, he is to discontinue all antihypertensive medications for that day and remain in bed until the faintness disappears. If the faintness has disappeared by the next day, he is to begin again at a *slightly* lower dose of the blocking agent, specifically a decrease of 10 to 20%. If the dose is drastically reduced, the antihypertensive effect will disappear. The aim, therefore, is to find the maximum tolerable dose, and this is frequently just below the one which produces symptoms of orthostatic hypotension.

4) Tell the patient to be cautious about drinking alcohol, as the latter in conjunction with blocking drugs may induce symptomatic hypotension. Strenuous exercise also may precipitate orthostatic hypotension.

5) Doses are titrated up to the effective level. The initial dose is small, but it is increased gradually until an antihypertensive effect or symptoms of orthostatic hypotension occur.

6) Reassure the patient that if orthostatic faintness or syncope occurs, it is not as serious as it seems; that it is equivalent to an ordinary faint, and that it can be avoided by proper regulation of dosage.

7) If the patient complains of orthostatic faintness, particularly in the morning, and if the office blood pressures are still elevated without a fall on standing, it may be either that the orthostatic effect disappears in the afternoon or evening, or else that the office recordings are abnormally elevated due to apprehension. If possible, the patient should visit the office in the morning when pressures are usually the lowest. Best of all is to have twice daily recordings taken in the home by a member of the family or the patient himself. Home blood pressure recordings are an invaluable adjunct in the treatment of severe hypertensive patients whose blood pressure levels are difficult to control.

*Relative Merits of Methyldopa, Guanethidine, and Pargyline*

Methyldopa is well tolerated because it produces less severe orthostatic hypotension and does not usually interfere with sexual function. It also depresses renal function less than guanethidine in patients with renal failure. On the other hand, it is effective in controlling blood pressure in only about half of the patients with severe hypertension. Three to four doses per day are required as compared to only one dose per day of the other blocking agents; it occasionally produces fever and hepatitis, and it is more expensive than the other drugs. Methyldopa is begun in a dose of 250 mg three times daily, increasing as necessary to a level of 750 mg four times daily. Elevations beyond this level generally produce little additional antihypertensive effect. The most frequent side effect is drowsiness, which is usually transient, tending to disappear after a stable dose level has been maintained for several weeks.

Guanethidine or Ismelin is begun in a dose of 10 mg once daily, and is increased every week by 10 mg until orthostatic hypotension or a reduction in supine pressure appears. In hospitalized patients or in those with severe hypertension, the doses can be raised more rapidly. The maximum dose is about 200 mg daily, although most patients will exhibit an antihypertensive effect in the range of 25 to 75 mg when thiazides are given adjunctively.

Guanethidine probably lowers blood pressure in a greater percentage of patients with severe hypertension than does any other drug. Dosage also is convenient since the total daily requirement can be taken once daily in conjunction with a long-acting saluretic agent. No hypersensitivity reactions or serious organ toxicity have been observed. Because it is a potent blocking agent, it is capable of inducing profound orthostatic hypotension. Once the dose is regulated, however, patients generally are not disturbed by this side effect. Diarrhea may be troublesome and usually calls for a slight reduction in dose. Atropine-like compounds, as well as paregoric, also can be used to combat this side reaction. While under the influence of adrenergic blockade, impotence occurs because orgasm is associated with ejaculation into the urinary bladder.

Another blocking agent in current use is pargyline or Eutonyl. Effective doses vary widely from as little as 10 mg to as much as 100 mg per day. If the latter dose is ineffective, larger amounts generally will not be effective. Pargyline is a monamine oxidase inhibitor and "psychic energizer." It does produce increased alertness and drive, sometimes to the point of inducing insomnia. Severe orthostatic hypotension can occur even in low doses. The onset of this latter effect may be delayed for several weeks or longer. For this reason, the doses should be gradually elevated with increases at widely spaced intervals several weeks apart.

*Patients taking monamine oxidase inhibitors may develop severe and even fatal hypertensive responses following the ingestion of processed cheese.* This unusual side effect is thought to be due to tyramine which is present in cheese.

It can be seen from this brief review that all antihypertensive agents are potentially toxic. The decision to treat a given patient, therefore, should not be undertaken lightly. To the risk of toxicity must be added the inconvenience and expense involved in lifelong treatment. An assessment of the average blood pressure and the extent of organic damage already present will help in separating those patients who require no treatment, and in determining in the remainder how intensive the therapeutic program need be. The death rates from hypertension, hypertensive heart disease, and cerebral hemorrhage appear to have been strikingly reduced since the advent of antihypertensive drug treatment. Therefore, this note of caution is not meant to discourage the application of antihypertensive agents, but rather to advocate care and discrimination in their use.

# Clinical Hemodynamics and Pharmacodynamics of Toxemia*

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For many years toxemia has served as a wastebasket for a variety of disease states characterized by an elevated arterial pressure, edema, and albuminuria. Whereas this triad is consistent with the diagnosis of toxemia, it is not diagnostic. Besides toxemia, these abnormalities may be found in pregnant patients with hypertensive vascular disease, pyelonephritis, glomerulonephritis, or any combination of these (fig. 1). Data derived from studies performed on patients with such a variety of disease entities have obviously been confusing. It makes a lot of difference, for example, whether the subjects studied had chronic pyelonephritis or acute vasospastic toxemia. During the past 13 years, our group has attempted to cut the pie of elevated arterial pressure, albuminuria, and edema into separate and distinct diagnostic pieces. Ophthalmoscopic examination and urinalysis have been of great help in this regard (Finnerty, 1954, 1956 and 1965; Finnerty *et al.*, 1960).

## Diagnosis

Toxemia was diagnosed when the ophthalmoscopic examination revealed spasm of the retinal arteries with no retinopathy, and urinalysis revealed only albuminuria (fig. 2). Hypertensive vascular disease existed when the retinal arteries were either normal or thickened and tortuous with AV nicking. When both signs of chronic vascular disease and acute vasospasm were observed with or without albuminuria, toxemia was then superimposed on hypertensive vascular disease. The finding of normal fundi and albuminuria suggested pyelonephritis. Clumps of cells in the urine and a positive colony count documented the diagnosis.

Figure 3 gives the diagnostic breakdown in 4,273 patients followed in our toxemia clinic during the past 3 years. It is interesting to note the frequency of pyelonephritis and hypertensive vascular disease, and the relative rarity of true toxemia. The recent biopsy studies of Altchek (1961) would seem to substantiate the finding that most patients originally thought to have toxemia actually have some other disease. The specific biopsy picture for toxemia has for the first time significantly clarified this wastebasket of syndromes. It would seem that toxemia is another type of glomerulonephritis. Figure 4 shows the similarity between toxemia and glomerulonephritis. Both diseases are characterized by a greater rise in the diastolic than the systolic pressure, which causes a narrow pulse pressure. The edema is particularly in the periorbital areas, hands and feet. Ophthalmoscopic examination reveals thread-

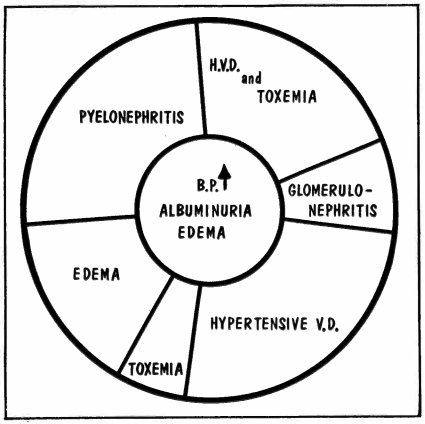


Fig.1.—Elevated blood pressure, albuminuria and edema are seen in toxemia but also in several other conditions.

* Presented at the Thirty-sixth Annual McGuire Lecture Series at the Medical College of Virginia, October 8, 1964.

**DIFFERENTIAL DIAGNOSIS OF TOXEMIA**

TOXEMIA < ELEVATED B.P. / ALBUMINURIA / EDEMA

| | OPHTHALMOSCOPIC EXAMINATION | | URINALYSIS | | |
|---|---|---|---|---|---|
| | Arterial Spasm | Retinopathy and A.V. Nicking | Alb. | W.B.C. | R.B.C. |
| *PURE TOXEMIA* | √ | 0 | √ | 0 | 0 |
| *H.V.D.* | 0 | √ | ± | 0 | 0 |
| *H.V.D. + TOXEMIA* | √ | √ | √ | 0 | 0 |
| *PYELONEPHRITIS* | 0 | 0 | √ | √ | 0 |
| *GLOMERULO-NEPHRITIS* | √ | 0 | √ | √ | √ |

Fig. 2—Ophthalmoscopic examination and urinalysis in the differential diagnosis of toxemia.

**THE DIAGNOSIS IN 4,273 PATIENTS**

1961 - 1963

| | | | |
|---|---|---|---|
| PURE TOXEMIA | 167 | 4% | 6% |
| TOXEMIA + HYPERTENSIVE VASCULAR DISEASE | 42 | | |
| TOXEMIA + PYELONEPHRITIS | 67 | | 25% |
| PYELONEPHRITIS | 704 | | |
| PYELONEPHRITIS + HYPERTENSIVE VASC. DISEASE | 287 | | |
| HYPERTENSIVE VASCULAR DISEASE | 804 | | |
| GLOMERULONEPHRITIS | 84 | | |
| NON-RELATED MEDICAL DISEASE (ANEMIA, HEART DISEASE, ETC.) | 214 | | |
| EDEMA WITHOUT DISEASE | 387 | | |
| ASYMPTOMATIC BACTERURIA | 469 | | |
| NO DISEASE | 944 | | |
| QUESTIONABLE DIAGNOSIS | 104 | | |
| TOTAL | 4,273 | | |

Fig. 3—Diagnostic features in patients attending the toxemia clinic

like arteries and generalized wetness of the retina. Both diseases are characterized by albuminuria.

### Pathologic Physiology

All the signs and symptoms of toxemia may be adequately explained by abnormal sodium retention and generalized vasoconstriction (fig. 5). The relationship between the two is unknown, but clinical observation attests that sodium retention usually precedes generalized vasoconstriction, and that prompt therapy of sodium retention usually prevents generalized vasoconstriction. The studies of Eisenberg (1959) in patients with acute nephritis, and Finnerty (1962) in patients with toxemia, show that there is an increase in plasma volume without an increase in circulating red cell mass. Following diuretic therapy the plasma volume returns to normal. This pattern of blood volume expansion, therefore, contrasts sharply with that in patients with congestive heart failure in whom there is a commensurate increase in red cell mass and plasma volume. These data suggest that an abnormality of salt and water metabolism is solely responsible for the hypervolemia of acute nephritis and toxemia.

A decrease in the amount of blood to a particular area due to increased vasoconstriction explains the remainder of the abnormality. An increase in cerebral vasoconstriction causes cerebral ischemia, leading to coma and convulsions. It is interesting in this regard to emphasize that it is cerebral ischemia, and not a rise in arterial pressure, that is the important abnormality in inducing coma and convulsions. The exact same symptoms may be caused by postural hypotension or an attack of Stokes-Adams syncope.

Evidence of both sodium retention and vasoconstriction, the two pathophysiologic abnormalities, can be visualized ophthalmoscopically. A wet, glistening appearance of the entire

**SIMILARITY OF GLOMERULONEPHRITIS AND TOXEMIA**

1. NARROW PULSE PRESSURE
2. LOCATION OF EDEMA
3. OPHTHALMOSCOPIC PICTURE
4. URINARY FINDINGS
5. RENAL BIOPSY

Fig. 4

retina (retinal sheen) and a decrease in the caliber of the retinal arteries characterize toxemia. The observation that the generalized sheen of toxemia is promptly decreased following diuretic therapy strongly suggests that it represents retinal edema.

Increased constriction of the peripheral vessels seems to account for the elevated arterial pressure. The increase in arterial pressure in toxemia is not associated in a change in the cardiac output. Finally, the increased vasoconstriction in the renal circulation, particularly in the afferent vessels as noted by Assali *et al.* (1953) accounts, in part at least, for the decrease in urinary output. The decrease in urinary output is part of the toxemic process and not necessarily a complication.

In summary, then, the toxemic process can be divided into two phases: the sodium retention phase, and the phase of sodium retention plus generalized vasoconstriction (fig. 6). The sodium retention phase is characterized by an increase in plasma volume which returns to normal following therapy. Prompt therapy will frequently prevent the development of the second phase.

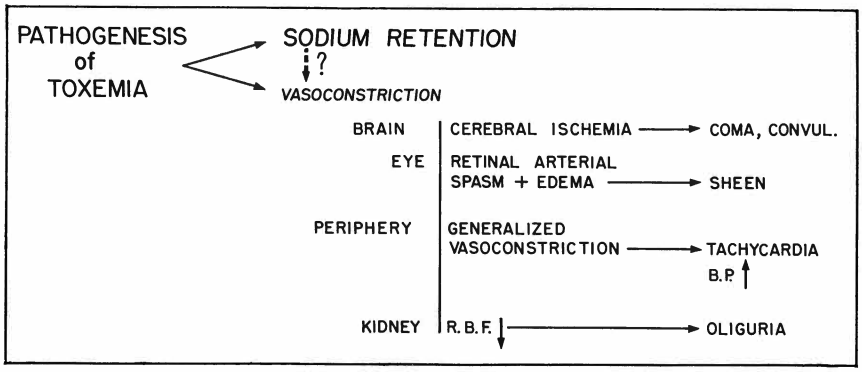


Fig. 5—Pathogenesis of toxemia

## Therapy

The availability of the thiazides has completely changed the concept of the treatment of toxemia. Prior to their development, the primary aim of therapy of toxemia was directed toward the control of arterial pressure and albuminuria (manisfestations of generalized vasoconstriction). Reserpine, hydralazine, and veratrum, therefore, were used extensively in our clinic, as well as in others. If the arterial pressure could not be lowered sufficiently, additional antihypertensive agents were added.

The primary aim of therapy of toxemia, at present, is prompt control of sodium retention. The effectiveness of the thiazides in immediately controlling abnormal sodium retention, and in returning the plasma volume to normal, has frequently prevented the development of generalized vasoconstriction and thereby practically eliminated the need of antihypertensive therapy in these patients. When used alone at the first sign of excessive weight gain, the thiazides frequently reverse the toxemic process. Even more important is the observation that they can be administered continuously without the development of drug resistance, thus preventing the development of vasoconstriction. For practical purposes, the prevention of vasoconstriction is equivalent to the preventing of toxemia. In our experience, these diuretic agents have resulted in more than a 70% reduction in the number of patients with toxemia during the past two years.

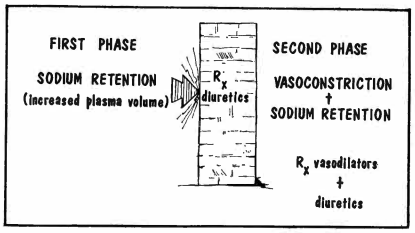


Fig. 6—Two Main phases of toxemia

If signs of vasoconstriction (retinal arterial spasm and albuminuria or either of them alone) are already present when the patient first presents herself, she probably should be hospitalized. It should be stressed that the primary aim of therapy in the hospitalized patient is preparation of the patient for delivery or Cesarean section. Whereas for the out-patient, sodium diuretics are the only agents needed, in the hospitalized patient these drugs serve only as background agents. Vasodilating agents must now also be administered.

We have recently had experience with a nondiuretic benzothiadiazine analogue whose structural formula is very similar to chlorothiazide (fig. 7). When administered by mouth it causes only a small reduction in arterial pressure, and also causes sodium retention and hyperglycemia. When administered by vein, however, it is a potent vasodilating agent. The average effective dosage is 300 mg (1 ampule) given rapidly, undiluted. To date, 69 patients with severe pre-eclampsia and 2 with eclampsia have received diazoxide with excellent results. The typical ef-

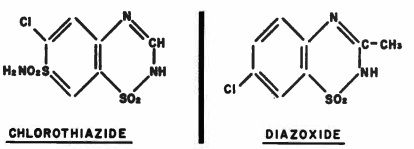


Fig. 7

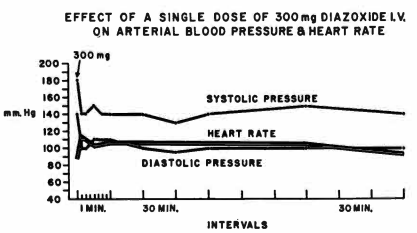


Fig. 8

fect of 300 mg of diazoxide can be seen in figure 8. A 35% average reduction in mean arterial pressure occurred during the first 2 minutes. During the next 3 to 5 minutes, the arterial pressure increased gradually, leveling off at 19% average reduction as compared with the control. No signs of postural hypotension, cerebral ischemia, or collapse were noted.

The fall in arterial pressure with diazoxide is consistently associated with an increase in cardiac output, and a decrease in total peripheral resistance. From the cardiac and cerebral hemodynamic standpoint, diazoxide resembles hydralazine since both agents cause an increase in cardiac output, heart rate, and cerebral blood flow. Actual cerebral blood flow determinations have not been performed in this laboratory, but the lack of signs of cerebral ischemia accompanying the reduction in arterial pressure, and the increase in cardiac output, strongly indicate that there is at least maintenance of the cerebral blood flow, even at the point of the greatest magnitude of hypotensive action.

Our experience thus far would indicate that diazoxide represented a real advance in the therapy of acute vasospastic hypertension.

## Prevention

Experience has shown that it is easier to prevent toxemia than to treat it. Although the thiazide diuretics seem to be the ideal agents for the treatment of the sodium retention phase of toxemia, their greatest asset is that they can be given continuously without the problem of drug resistance. I feel, therefore, that the thiazides should not only be given at the first sign of sodium retention, but should be instituted from the tenth week of pregnacy in patients who are candidates for toxemia, e.g., patients with chronic hypertensive vascular disease, patients with chronic renal disease, and probably all primagravida patients. The data on more than 6,000 patients treated with thiazides has shown that the continued use of these drugs following the tenth week of pregnancy apparently is not harmful to the fetus.

## References

ALTCHEK, A. Electron microscopy of renal biopsies in toxemia of pregnancy. *J. Am. Med. Assoc.* 175: 791–795, 1961.

ASSALI, N. S., S. A. KAPLAN, S. J. FOMON, AND R. A. DOUGLASS. Renal function studies in toxemia of pregnancy. *J. Clin. Invest.* 32: 44–51, 1953.

EISENBERG, S. Blood volume in patients with acute glomerulonephritis as deetermined by radioactive chromium tagged red cells. *Am. J. Med.* 27: 241–245, 1959.

FINNERTY, F. A., JR. Does vascular damage follow toxemia of pregnancy? An internist's appraisal of three hundred three patients in a toxemia clinic. *J. Am. Med. Assoc.* 154: 1075–1079, 1954.

FINNERTY, F. A., JR. The significance and treatment of blood pressure elevation associated with toxemia of pregnancy and acute nephritis. *Am. J. Cardiol.* 9: 888–892, 1962.

FINNERTY, F. A., JR. Toxemia of pregnancy as seen by an internist: An analysis of 1,081 patients. *Ann. Internal Med.* 44: 358–375, 1956.

FINNERTY, F. A., JR. Pyelonephritis masquerading as toxemia of pregnancy. *J. Am. Med. Assoc.* 161: 210–214, 1956.

FINNERTY, F. A., JR., W. D. FOOTE, G. DEC. MASSARO, J. TUCKMAN, J. H. BUCHHOLZ, AND M. J. RYAN. The significance of lateral and generalized retinal sheen. *Ann. Internal Med.* 52: 819–826, 1960.

# Panel on Arteriosclerosis*

WILLIAM DOCK, MODERATOR

*Dr. William Dock* (professor of medicine, Downstate Medical Center, State University of New York): One of the points I should like to make, is that smoking acts on the circulation only by the absorption of nicotine. It has nothing to do with the smoke. In other words, to get on the wrong side of the cook-out fire will not increase much the risk of coronary disease, although it might give you bronchial carcinoma after 50 or 100 years. Nicotine acts much as though the individual who smokes a cigarette or gets a good chew of tobacco had been given a good intravenous infusion of epinephrine or norepinephrine. The free fatty acid goes up, the blood pressure goes up, and the stroke volume goes up. The stresses produced on the circulation by nicotine are exactly like those produced by catecholamines. While you can change to chewing or switch to a pipe to get rid of obstructive emphysema, the effects of nicotine on the coronary vessels will be the same no matter how you absorb it. We assume the effects of smoking on coronary disease are what you'd expect if the patient were getting infusions of epinephrine during the day, at regular and very frequent intervals. Caffeine also apparently acts in somewhat the same way. Of course, Coca-Cola does, too. Any of these things can accelerate atherosclerosis some. As the people in Cincinnati have reported repeatedly, and as the nicotine symposium held in New York at the National Academy of Sciences strongly emphasized, chewers of tobacco have much worse vascular disease in the legs and much more coronary disease, age corrected, than two-pack-a-day cigarette smokers. Of course, they get the most nicotine for their money. If you want nicotine, and they want nicotine, there is a price to pay when you are on the North American diet. On the other hand, presumably, a tobacco smoker in North China runs no additional risk of coronary disease, because he runs no risk to begin with.

*Dr. William Hollander* (associate professor of medicine, Boston University School of Medicine): Dr. Dock, could I perhaps comment on the effect of catecholamines on the metabolism of the arterial wall? We have some observations regarding the effects of norephinephrine on our incubated arterial tissue, including atherosclerotic tissue. What we have been finding is that, as you have indicated, catecholamines stimulate the lipoprotein lipase activity in atherosclerotic tissue. Consequently, the triglyceride content falls off very strikingly within a period of four hours. You can actually measure a drop in the lipid content in these arterial walls.

What about Buerger's disease? This disease can be aggravated by smoking. I do not know what the *in vivo* effects of norepinephrine are in Buerger's. And anyway, in Boston the pathologists say that there is no difference between Buerger's disease and ordinary atherosclerotic disease of the legs.

*Sir George W. Pickering* (regius professor of medicine, Oxford University): Could I disagree with that? I have been concerned with people with vascular disease of the legs ever since I went to work with Sir Thomas Lewis. These two diseases are quite different clinically, whatever they are like histologically. Buerger's disease is a disease of young men which is practically unknown in females, and it stops like that if you stop smoking. The influence of tobacco on Buerger's disease is, I think, 100%.

*Dr. Dock:* Early Buerger's arteries are full of lipid only with the North American diet of the present time. When you get syphilis, or when you get Buerger's disease, you get atherosclerosis on top of it because of our diet. In the regions where people don't get highly fatty diets you can see pure Buerger's, and you can see pure syphilitic aortitis without atheroma.

Well, we don't want any of our patients to get syphilis and we hope they all will stop smoking. The smoking influence is so clear-cut in statistical studies that it is a tragedy that it is easier for a patient to have blood drawn every week to see how his prothrombin is doing, and take Coumadin pills, than it is for him to stop buying tobacco. Tobacco is an extremely addicting drug, probably as addicting as morphine. And the physiological damage done by tobacco or nicotine is certainly much worse than that done by morphine. If you don't smoke opium, you don't get obstructive emphysema from it. If you take morphine in little pills, it makes you feel good just the way smoking does, but it does not produce the catecholamine effect, and there is no evidence that it produces arteriosclerosis or even aggravates it. So, we are hoping to get the Narcotic Act repealed! Everybody on the panel but me and Dr. Stamler, I think, are two-pack-a-day or nine-pipe-a-day smokers. You see how hard it is to stop the addiction. Dr. Pickering and I knew three full professors of medicine in leading American universities who died of obstructive emphysema. Not one of these men could cut down his smoking though he knew he was headed for the boneyard. One of them used to sneak into his garret and smoke so his wife could not catch him, and this was after he had been in the hospital and in a helium tent. So, we have agreed on the panel that you cannot give up smoking, and most of us agree, I think, that patients cannot be persuaded to stay on diets. Dr. Stam-

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ler, can they be persuaded?

*Dr. Jeremiah Stamler* (director of the heart disease control program, City of Chicago Board of Health): The question is not whether people can be persuaded to stay on a diet. I think the question is whether a population can change its eating habits sufficiently to alter the pattern of a disease. If what we are really talking about is meaningful and important, it has a whole lot of sociological consequences which come into play beginning with the earliest period of habit formation, in the time of weaning. I was talking with Dr. William Harlan about what happens to young men in America. They are very active in athletics, they develop the training table or the basic training pattern of eating. Then they stop physical activity when they cease to be active in athletics or leave the armed forces, but they keep on eating the same way. Or, even worse, they fall into the hands of a wonderful, lovely little girl who wants to show that she learned the right things from Mamma about cooking.

*Dr. Dock:* Now, Dr. Pickering, I think we should give you a chance to get back into the argument. In the first place, does your group feel that diet has any importance whatever in the pathogenesis of vascular disease?

*Prof. Pickering:* As August Krogh once remarked, "Physiological phenomena are so complicated that, if you argue from more than one step to another without the control of experiment, you are almost certain to go wrong." Before I would be prepared to encourage a mass change of diet, I would like to have a pilot study to see that this mass change was doing a certain amount of good. If I remember rightly, there is a certain well-known professor of medicine who put himself on a very rigid low-fat, no cholesterol diet, and has since had a cholesterol stone removed from his gall bladder.

*Dr. Dock:* And you conclude that it formed after he went on the diet?

*Prof. Pickering:* Well, he may have had it before, that is perfectly true.

*Dr. Dock:* I think that Dr. Pickering has brought up a very important point. A man with asymptomatic gall stones who goes on a diet with vegetable oil is very likely to have his stones decrease in size to where they can slip into the cystic or common duct. Then he will have his first attack of colic one, two, or three years after he has cut his cholesterol intake, because the stones will get smaller and give symptoms. I have had three such patients. One of them had his gall stones taken out at Peter Bent Brigham Hospital after his fifth attack of colic. His first attack came on about three years after he changed his diet. Fortunately he had had his gall bladder visualized eight years before, and beautiful, big cholesterol stones had been seen, far too big to get into his duct.

I think that if you try to starve too fast, you may run your serum triglycerides up quite high by starvation. People have their first bout of myocardial infarction just after they have gone on a marked weight reduction program. This has been noted over and over again. There is a great craze now in parts of the United States for starvation as the way to start a weight reduction program. It can be predicted that this should up the incidence of coronary disease in the first three months after you go on that sort of program. Whether it will, I don't know.

I think that physicians who feel, as Dr. Pickering and his group do, that the role of diet in vascular disease is not yet established, should say as much to their patients. This seems to me to be perfectly sound, rational management.

On the other hand, Pickering is a doctor who thinks perhaps Harvey was right in saying that if animal experiment indicates that the blood circulates, then it may circulate in man. If you take animal experiment as being relevant to human physiology and pathology, and you know that dietary manipulation will produce vascular disease in chickens, rats, guinea pigs, rabbits, dogs, hamsters, monkeys, and pigs, it does become a little awkward to say, "Well, we don't believe that animal experiment is relevant to human experience in this particular field." It is perfectly sound doctrine to say this, as it was for Dr. Sydenham to say, "Just because Harvey thought that blood circulated in a snake or a deer is no reason to think that blood circulates in man." To me, this is perfectly sound, rational argument. Sydenham was the greatest internist of his generation. You can be a great man in your generation, and it may turn out that you were right. Or, it may turn out that you did not take as seriously as you should have the data that were available.

*Prof. Pickering:* Yes, there is a little difference, though. You will recall that Krogh said, "If you argue from one set of data to another without the control of experiment you are likely to go wrong." And I believe that there is a difference between the rabbit and the human being. The diet that rabbits eat in experiments is very different from the diets that they ordinarily eat. And the lesion which is produced in rabbits is not quite the same as the lesion which produces myocardial infarction in men. And so, I think your reasoning will not hold up at every point, and even if it did, man is a different species from rabbit. I would like to see the effect of diet demonstrated in man before I am prepared to believe it is effective in controlling vascular disease.

*Dr. Dock:* Well, this experiment is under way in the United States at enormous expense at the present time.

*Dr. Stamler:* Could I just say a word about this? I didn't get to hear Sir George, but I have read some of his writings, and I had the good fortune to hear the tape of his lecture earlier in this symposium. I'd like to dismiss one or two of the arguments which I don't think are entirely valid, or, if not dismiss them, at least put them on the table for rediscussion. The first is the question of the rabbit as an atypical species. The second is the matter of drowning the animals in very high cholesterol, high fat diets. Both of these were problems in 1948. I do not think either is much of a problem now for the following reasons: 1) The disease has, in fact, been reproduced, with a lesion remarkably similar to the human lesions, in a wide range of species, as Dr. Dock said. So the problem that did confront workers in the 1930's, that of the ability to reproduce the disease only in the rabbit or guinea pig, is no longer entirely true. In fact, quite the opposite is true. We have the dog, rat, chicken, rabbit, and a variety of monkeys. The monkey experiments have been done using diets similar to the human diet, in fact, feeding human

foods in periods that correspond to a life span equivalent to human beings. These produced moderate elevations of the serum cholesterol level in the 200's and 300's, peripheral gangrene, myocardial infarction, and cerebral infarction.

On the question of experiment in man, I would like to add a word to that. As practicing doctors, I think that the profession has a very difficult problem. Let's face it, these studies in the population may not come off. If they do come off, they will take a decade at least to get an answer. And what does one do in the interim, wait for the results of the experiment, and say, "Well, we're not sure." That's OK, but every physician who makes that decision has to accept the corollary of it, and even has to tell his patient of the corollary. "If you are a high risk, middle-aged American man, I have very little to offer you while I'm waiting for the purity of a scientific answer." Because, really, we do not have much to offer aside from our approach to these risk factors, of which diet, blood cholesterol, and weight are three key ones. If we are prepared to accept that corollary, and transmit it to our patients, then I say we can wait for the big experiment, if it ever gets done. If not, I think we should intervene in a safe way.

*Prof. Pickering:* Well, that is what I think I said. If the doctor, himself, does not believe in this, he should tell his patients he does not believe in it. If they want to go on the diet, he is glad to direct them. If he does believe in it, he has got to practice what is known as the Golden Rule and say, "If I had your trouble, this is what I would do. . . ." I think this is the best any of us can do. The same thing applies to the use of anticoagulants. If the patient says, "Well, would you take this yourself?" I have to tell him that I hate to have my arms stuck every week, and for a difference in mortality of 4% as against 5% a year, roughly, I don't believe I would take all of this trouble.

Dr. Stamler and I have rather different views about atherosclerosis, I think. He would include a lot of lesions that I suspect are not the same.

*Dr. Stamler:* I include only lesions with porridge in them—no lipid, no atherosclerosis, as far as I am concerned. Patients who have been starved have fibrous plaques and calcium, but no demonstrable lipid when they die. It is true in man that the lipid can disappear so you see only the scar of the disease. If I had to limit the diagnosis of syphilitic aortitis to people in whom I could demonstrate treponemes, I would be out of luck, because penicillin has killed the treponemes in all of my patients. Just as I diagnose former syphilitic aortitis from sections, I now diagnose former atherosclerosis at autopsy in patients who, as a result of leukemia, say, have lost a great deal of weight and been markedly undernourished through periods of about two years before they died. So you can lose the lipid from plaques, I'm sure. Furthermore, I believe that lipid is present in the lesions of adolescence in larger quantities than it is in the lesions of men of 40, and is present in larger quantities in men who die at 40 than it is in men who die at 70. These are my own views. This is almost a question of religious experience. Dr. Pickering belongs to one church, and has had one religious background in this field. I belong to a different church, having had different clergymen working on me in my youth. So, I don't expect to convince Professor Pickering that the lesions I showed in small vessels are related to the lesions that the same patients had in their coronary arteries, although both of those patients from whom I showed you sections were hypertensives with hypercholesterolemia who died of myocardial infarction. They had lesions in small arteries. Dr. Pickering thinks these are unrelated to the lesions in the coronaries. I cannot see why they might not be the same lesions.

*Prof. Pickering:* Well, I think they are different. Partially because they look different, and partially because, in the small arteries, kidney, and in the retinal arterioles, lesions are much more closely correlated with the height of the arterial pressure than is the disease I was talking about which produces big nodules in arteries like the carotid, and ultimately leads to thrombosis of them.

I will not agree with Dr. Dock that, because you can see lipid in them both, they represent the same disease. He says we belong to different churches. I

think he does belong to a church. I am just a plain agnostic.

*Dr. William R. Harlan, Jr.* (director of clinical research center, Medical College of Virginia): It is much easier to make long studies of large series of cases with a drug than it is with a diet, and I think this may turn out in the end to be a more profitable way of shedding light on what the plasma lipid has to do with arteriosclerosis in man. It will not settle whether plasma lipid acts by accelerating coagulation, but at least it would cast some light on whether changing the lipid levels in the plasma would improve the prognosis.

We ought to ask Dr. Stamler about estrogens and the drug androsterone, which we produce in our bodies—a very weak androgen but it tends to lower blood cholesterol. These two agents can be given to lower plasma lipid, at least plasma cholesterol levels, in male patients. Are you still carrying on estrogen studies?

*Dr. Stamler:* In brief, there are three reports of a controlled nature on the estrogens in post-myocardial infarction in man. One of them is a British study by Oliver and Boyd that deals with 100 patients up to age 65. Another is an American study that deals with men of all ages on lower doses of mixed conjugated equine estrogen. Oliver and Boyd used ethanyl estradiol. The third study is by our group in Chicago, using mixed conjugated equine estrogens in men under 50. In the 100 patients whom they studied, Oliver and Boyd got completely negative results, although serum cholesterol levels were lower. The Los Angeles study with lower doses of mixed conjugated equine estrogen is still in progress, but there are positive results, particularly in the patients under 50. I think none of these studies to date permits a clean-cut decision on the efficacy of estrogens. I might note that there is a peculiar aspect to the estrogen work; while ethanyl estradiol consistently lowers total blood cholesterol level, mixed conjugated equine estrogens do not. They shift the lipoprotein pattern, but they do not consistently lower the total cholesterol level. They raise the $\alpha$- and may lower the $\beta$- proportionately, so that total cholesterol changes very little. They do, unquestionably, convert the $\alpha$- from a male level of about 50 or so to a female level of 250, 300, 350, or greater. Whether this is efficacious is, of course, moot.

*Dr. Dock:* One of the questions is whether a reduction in blood pressure will help us have a lower incidence of cardiovascular disease. I think you believe it will.

*Prof. Pickering:* No, I don't believe it will. I think the evidence suggesting this is bad.

*Dr. Dock:* You said that in severe hypertensives, lowering blood pressure changes the whole course of the disease. If this is true, how can it help but lower the death rate?

*Prof. Pickering:* Oh, I thought you were talking about arteriosclerosis.

*Dr. Dock:* No, no. In any sort of vascular disease, will lowering the blood pressure improve the prognosis?

*Prof. Pickering:* Well, it depends on how high the blood pressure is. If the blood pressure is very high, or if you get a patient in the malignant phase before the kidneys are really very severely involved, then I think the evidence is quite clear that you can prolong the expectation of life.

*Dr. Dock:* But in a patient with a lower level of blood pressure and with a myocardial infarct, is it worthwhile to try to lower the blood pressure?

*Prof. Pickering:* No, I would not say that. But I think that I have distinguished what I would regard as established, and what I would regard as a sufficient degree of probability, so that I would use it in the treatment of my patients. I do not regard it as established that diet will reduce the prevalence of myocardial infarction, but instead, I do advise my patients: 1) to try to regain their youthful figures, 2) to substitute corn oil for their ordinary cooking fat, 3) to take as much exercise as they conveniently can, 4) if their arterial pressure is high, I reduce it, and 5) if they are under 55 and male, I put them on anticoagulants, but I do not ever go very high with them, because I am afraid of them. I do not use anticoagulants in patients with peptic ulcer, gross hypertension, or liver disease.

*Dr. Dock:* Well, I think with this useful advice, perhaps we had better bring the meeting to a close.

# Rheumatic Fever: Natural History and Treatment*

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Major advances in clinical and laboratory research methods have significantly clarified the identification and natural course of rheumatic fever in the past two decades. The advances in methodology include the following:

### Diagnostic Purity of Population

The label of *rheumatic fever* is now given to a population of patients more distinct and diagnostically "pure" than ever before. The Jones criteria, described in 1944 and modified in 1956 (American Heart Association, 1956), circumscribe the diagnostic boundaries of the disease, and exclude many minor illnesses that formerly were designated inappropriately as rheumatic fever. Other major illnesses that once successfully masqueraded as rheumatic fever, because they fulfilled the Jones criteria, can now be unmasked and properly identified by specific laboratory tests (such as those used for lupus erythematosus, rheumatoid arthritis, and sickle cell anemia) and by cardiac catheterization (for congenital heart disease). These diagnostic purifications improve the homogeneity and reproducibility of a population of patients with rheumatic fever, thus improving the reliability of conclusions drawn from observations of the population.

### Spectrum of Post-streptococcal Inflammation

The frequent sequential testing of multiple streptococcal antibodies (a laboratory technique developed mainly in the past two decades) has demonstrated not only that acute rheumatic fever is constantly associated with Group A streptococcal infection, but also that rheumatic fever is merely an arbitrarily defined collection of events in the complex clinical spectrum of inflammation which can follow streptococcal infection. Within this spectrum, the main events used to identify rheumatic fever are arthritis, chorea, or carditis—occurring alone, in various combinations, or concomitantly with other clinical features. Because so many different combinations of events can receive a diagnosis of rheumatic fever, the clinical manifestations of the disease demonstrate many apparently disparate patterns. The differences in these clinical patterns (Massell, Fyler, and Roy, 1958; Feinstein and Spagnuolo, 1962) were responsible for much of the past confusion in assessing etiology, pathogenesis, and prognosis. Some of the unclear issues recently resolved are noted below:

#### *Isolated Chorea*

The latent interval after a streptococcal infection is usually much longer for Sydenham's chorea than for other "rheumatic" manifestations. Chorea may therefore often appear as, or after, other types of clinical rheumatic inflammation subside. Or it may occur alone, i.e., as "pure" chorea, long after the streptococcal antibody titers have receded to a level too low to permit detection of the antecedent infection.

#### *Asymptomatic Carditis*

Carditis, another type of inflammation that can occur in the post-streptococcal spectrum, is ordinarily asymptomatic if unaccompanied by significant fever or by congestive heart failure. When carditis occurs alone without symptoms created by arthritis, chorea, fever, or cardiac complications, the carditis will not be examined while it is acute because the patient will not seek medical attention; carditis can thus produce its valvular scars silently. When the scars are discovered many years later, rheumatic heart disease is said to have occurred without a "history of rheumatic fever." This type of rheumatic heart disease is undetected clinically and develops insidiously only because the patient is not examined during the acute phase of the carditis. Had the patient been symptomatic enough to seek medical attention, the signs of carditis could have been found. The failure of clinicians to find such patients early is thus a fault neither of clinicians nor patients; it is attributable to the natural behavior of the disease. When post-streptococcal inflammation produces acute carditis asymptomatically, it is clinically unexamined and hence undetected.

#### *Severity of Symptoms and Promptness of Therapy*

Although pathologists, from examination of tissue, have long known that rheumatic fever "licks at the joints and bites at the heart," the *clinical* validity of this maxim, and of its converse has only recently been demonstrated (Feinstein and Spagnuolo, 1962). The patterns of clinical behavior in rheumatic fever show that patients with severe arthritis are quite commonly free of carditis, and those with carditis severe enough to produce congestive heart failure often have no joint symptoms. This inverse relationship between the clinical severity of arthritis and carditis is a feature of natural history that creates a thera-

* Presented at the Richmond Area Heart Association Symposium on Cardiovascular Diseases, February 10, 1965, at the Medical College of Virginia. A few weeks earlier, Dr. Feinstein gave this report before the Second National Conference on Heart Disease in Washington, D. C.

peutic paradox in the disease. The main reason that residual rheumatic heart disease occurs less often in patients treated soon after onset of symptoms than it does in those treated late is that most patients who seek treatment early usually do so because of arthritis. They have little or no carditis to begin with. Conversely, the late-treatment group consists predominantly of patients whose solitary carditis took a long time to produce symptoms severe enough to make the patients seek medical aid. In such patients, the cardiac damage when first found is usually too great for cure by anti-inflammatory therapy (Feinstein, Stern, and Spagnuolo, 1964b). The natural behavior of the illness, rather than the treatment, is thus responsible for many of the successes in which no heart disease is found after early therapy.

## Clinical Identification of Carditis

The assessment of the noises and shadows used as evidence of carditis has markedly improved in the past two decades by recognition and removal of several older diagnostic impediments:

### *Reliability of the Examiner*

The reliability of the clinical examiner who observes and appraises the audio-visual evidence of cardiac status has been greatly improved by use of objective, "blind," examining techniques, multiple examiners, precise descriptions, and rigorous criteria for interpretation. These improvements in the scientific performance of the clinician have been aided, and sometimes evoked, by modern methods of roentgenography and phonocardiography. As a result of these clinical and technical improvements, better methods and criteria (Feinstein *et al.*, 1964a and c) have evolved for avoiding two types of observational error (described in the next section) that formerly created confusion in identifying the status of patients, evaluating the results of therapy, and understanding the pathogenesis of rheumatic valvular disease.

### *Observational Errors and their Consequences*

Errors can be expected during clinical examination of the heart. Errors of commission, in which physiologic phenomena are mistakenly regarded as pathologic, often arise in making the diagnostic distinctions between: physiologic systolic murmurs loudly audible at the apex and those of mitral regurgitation; long physiologic third heart sounds and diastolic murmurs; split first sounds and presystolic murmurs; artifactual curvature of the barium esophagram and left atrial enlargement; physiologic variations in the roentgenographic cardiac silhouette and those due to cardiomegaly. As a result of such errors of commission made during an acute rheumatic attack, "carditis" initially would be diagnosed falsely and its "cure"—when the true physiologic state was eventually recognized—would later be attributed inappropriately to therapy. At a subsequent examination of a patient previously (and correctly) deemed free of carditis during the acute attack, such errors would lead to the spurious belief that rheumatic heart disease had developed insidiously.

An error of omission occurs when a pathologic phenomenon is undetected, or mistakenly regarded as physiologic. Such errors commonly arise from failure to recognize an aortic diastolic or apical presystolic murmur when it is present, particularly in situations where suspicion of the murmur is not aroused by concomitant hemodynamic or roentgenographic abnormalities. If the abnormal murmur persisted and eventually were identified correctly, rheumatic heart disease would be said to have developed insidiously in a patient believed to be free of it.

The improved modern auscultatory procedures described earlier have reduced the incidence of both types of error, and accordingly, have reduced the number of patients considered to have developed rheumatic heart disease insidiously. Recent data (Feinstein *et al.*, 1964a, b, and c; American Heart Association, 1960) have shown that insidious rheumatic heart disease develops *de novo* primarily in patients who were asymptomatic and unexamined while they had acute carditis, and not in those examined during arthritis or chorea and found free of valvular involvement.

### *Clarification of Ancillary Tests for Carditis*

Holding the belief that many noncarditic patients might later develop insidious rheumatic heart disease, clinicians had avidly searched for diagnostic aids to find evidence of the carditis that appeared to be clinically undetectable. Chief among these aids were the electrocardiogram and several laboratory tests. Although the original search for these indices of undetectable "subclinical" carditis was based on a premise that was itself not valid, the lack of validity in the existing ECG and laboratory tests for carditis has been demonstrated independently. Prolongation of the P-R interval, once regarded as a manifestation of carditis, occurs in about one-third of patients with post-streptococcal inflammation, regardless of concomitant clinical evidence of acute carditis. Moreover, in careful long-term studies (Feinstein *et al.*, 1964a, b, and c; American Heart Association, 1960), acute P-R prolongation has been shown to have no prognostic significance. Alteration of the $QT_c$ interval, an observation whose value was never proved initially, has now been abandoned as an index of acute rheumatic carditis. Changes in electrocardiographic T waves of young patients—particularly in III, in aVF, and in the transitional precordial V leads—were once regarded as evidence of carditis, but are now interpreted with skepticism. Because of normal variations in the anatomic position of the heart during respiration and with different phases of the cardiac cycle, and because of inconsistent placement of the external probing electrode, T-waves can vary greatly from one to another of the repeated ECG's taken in children and adolescents during a rheumatic episode. Of the various laboratory tests popularized in the past 10 years, none—despite a transient, later discredited, enthusiasm for transaminase—has convincingly been demonstrated to be a specific, reliable index of carditis. Consequently, cardiac noises and roentgenographic shadows remain the major variables that indicate carditis clinically, and the physician remains the major apparatus for assessing these variables.

## Clinical Course of Acute Rheumatic Fever

For reasons already cited, no single clinical pattern can be properly representative of all the ways in which rheumatic fever can appear and evolve. The patterns are composed, however, of individual clinical manifestations that often do have typical courses. Untreated rheumatic arthritis generally lasts no more than several weeks, sometimes no more than a few days, and leaves no residual defects. The knees and ankles are affected most commonly; elbows, wrists, and hips are involved less often. Although small joints of the hands and feet, and the vertebral or temporo-mandibular joints may be affected uncommonly in rheumatic fever, an alternate arthropathic condition should always be considered and ruled out when these joints are involved. The arthritis of rheumatic fever often can involve only one joint, or several joints simultaneously. The development of migratory and polyarticular arthritis, polyarticular arthritis alone, often depends upon the severity of the attack, and the promptness with which bed rest or anti-inflammatory treatment is begun.

Like arthritis, Sydenham's chorea also leaves no permanent defects, although the young patient may develop many psychologic scars from scholastic deprivation and from anxieties that the peculiar movements of the chorea may induce in him or in the people who deal with him. The duration and severity of chorea vary unpredictably in each patient, making an effective evaluation of therapy difficult. Some attacks last only a few weeks, while others last three or four months. The movements are rarely so severe as to threaten the patient's safety, and often they do not impair ambulation; most commonly the patient is able to walk but cannot write, dress, or feed himself. Erythema marginatum seldom lasts more than one or two days—sometimes only a few hours—and, like chorea, it often occurs late in a rheumatic attack. It can sometimes occur early, however, but rarely alone. Subcutaneous nodules are seen much less frequently today than in the past (the reasons for the change are unknown) and almost never occur alone without some other rheumatic manifestation. The nodules most commonly are associated with carditis, and often with severe carditis.

If carditis occurs in a particular attack, the evidence is usually present when the acutely ill patient is first encountered in the hospital (Massell *et al.*, 1958; Feinstein and Spagnuolo, 1962). After hospitalization, a patient admitted with significant murmurs may develop additional new murmurs, rubs, changes in heart size, or congestive heart failure, but significant murmurs will seldom appear if none were present during the first two weeks of observation. In the most common situation, the patient's carditic manifestations are at their worst when he is hospitalized, and they then persist or subside during the ensuing acute course of the illness.

The belief that acute rheumatic fever was often a "polycyclic" illness has also been revised in recent years. If untreated, an episode of rheumatic fever usually follows a course of gradually declining inflammation, in which laboratory abnormalities last longer than clinical ones, except for chorea. The sedimentation rate reaches normal levels in an average of three months for patients without carditis, and in four months for those with carditis. Once a rheumatic attack has begun, anti-inflammatory treatment can suppress some of the manifestations of the inflammation, but the treatment does not repair the damage done to the heart. The attack may be followed by rebounds that represent an outlet for the inflammatory stimulus that remained dormant during the preceding suppression of inflammation (Feinstein and Spagnuolo, 1961). Post-therapeutic rebounds are one of three mechanisms by which acute rheumatic inflammation can recrudesce. A second mechanism is a recurrence of acute rheumatic fever, provoked by a new streptococcal infection. A third mechanism, still poorly understood, is present in about 5% of patients with rheumatic fever. In these patients, the acute attack is excessively prolonged or "chronic," with clinical and laboratory evidence of acute inflammation present for more than eight months in the absence of an intervening streptococcal infection. Unlike post-therapeutic rebounds, the exacerbations of inflammation in these "chronic" attacks show no temporal relationship to preceding suppressive treatment. "Chronic" attacks are most likely to occur in patients with severe cardiac damage and in those who have had many previous episodes of rheumatic fever (Taranta, Spagnuolo, and Feinstein, 1962).

## Long Term Sequelae of Rheumatic Fever

Great improvements have been produced in the past two decades in epidemiologic methods for careful long-term observation of patient populations having identified attacks of rheumatic fever. Several recent large-scale studies (Feinstein *et al.*, 1964a, b, and c; American Heart Association, 1960) of rheumatic sequelae have been performed by cooperative efforts of different groups of investigators or by single institutions, and have shown the following results:

(a) Patients initially free of clinical evidence of carditis remain essentially free of it thereafter. Rheumatic heart disease remains in about 9% of patients with equivocal initial evidence of carditis.

(b) In patients with congestive heart failure or marked cardiomegaly in the acute attack, evidence of cardiac damage seldom disappears. Patients with such severe carditis are the usual source of those who die at an early age. If they survive the acute rheumatic episode, the patients with severe acute carditis often die later as a result of the remaining cardiac damage, and not necessarily because of persistent or recurrent active rheumatic inflammation.

(c) Significant murmurs later disappear in about 40% of patients who had murmurs but no cardiomegaly or decompensation during a rheumatic attack. The disappearance of murmurs is most likely to occur in patients with systolic rather than diastolic murmurs, with murmurs of one valve rather than two, and with no previous episodes of rheumatic fever.

(d) Except for a small percentage of patients incapacitated by cardiac symptoms, most rheumatic patients have no clinical impairment of cardiac function during adolescence, even though signs of major cardiac damage may be present. Restriction of scholastic or

physical activities in such asymptomatic patients appears to have no medical benefits and may create adverse psychosocial reactions (Feinstein *et al.*, 1962).

(e) Recurrences of rheumatic fever may make cardiac damage worse in patients who already have it, but do not generally bring valvular damage to patients previously free of it. In patients without previous valvular damage, a recurrence is often manifested by arthritis, chorea, or occasionally pericarditis, but seldom by persistent new valvular murmurs.

### Treatment of Acute Rheumatic Fever

Although the many studies of therapy of acute rheumatic fever performed in the past decade have helped clarify the course of the disease, they have not reached uniform or consistent agreement about the value of steroid treatment. The main difficulty has been the absence of reproducibility in the different methods used to allocate patients initially into comparable sub-groups of the rheumatic spectrum, and to identify the presence and disappearance of carditis (Feinstein, 1961). At present, steroids have not been proved superior to salicylates in the routine treatment of rheumatic fever, nor has either of these agents been proved consistently more effective than no treatment. Patients without carditis usually emerge free of heart disease, and those with severe carditis usually have residual heart disease, regardless of the mode of treatment. The comparison of therapeutic agents is thus best restricted to patients with "mild" carditis, i.e., murmurs only. In such patients, current therapeutic results are inconclusive because of lack of uniformity in the identification of murmurs by different investigators.

Despite the many therapeutic controversies, certain approaches are accepted almost unanimously:

(a) A course of antimicrobial agents adequate to eradicate streptococci should be given when the diagnosis of acute rheumatic fever is established, even though throat culture and ASO titer are normal. Massive doses of antibiotics for long periods of time have not been proved more effective for therapy of rheumatic fever than an ordinary streptococcal-eradicating regimen.

(b) Patients without clinical evidence of carditis can be made comfortable by salicylates or analgesics, and do not require steroids.

(c) Chorea is a yet unsolved therapeutic enigma, with no consistent success obtained by any of the various sedatives, tranquillizers, and anti-inflammatory agents that have been tested.

(d) Steroids are unequivocally better than salicylates in a small percentage of rheumatic patients who have overwhelming decompensated carditis, and whose inflammation can not be controlled with salicylates. In these situations, the steroids do not seem to repair any of the damage left by the rheumatic fire, but save the heart from immediate acute destruction by the fire, even though the severe residual damage may lead to death a few years later.

(e) In ordinary mild carditis, steroids have no unequivocally demonstrable superiority to salicylates. The main advantage of steroids is a more rapid clinical and laboratory disappearance of certain non-cardiac inflammatory abnormalities; the main disadvantage of steroids is the frequent development of cutaneous striae (in young patients) during treatment and the common occurrence of rebounds after treatment. The rebound phenomenon after steroids can often be eliminated or minimized by giving salicylates as overlap treatment, starting on the date of reduction in steroid dosage and continuing for at least several weeks after steroids are stopped.

These clarifications in our knowledge of natural history of rheumatic fever have come from better understanding of properties of the streptococcus and of the clinical reactions it elicits in its human host. The next two decades of research should help to clarify the reasons and mechanisms for susceptibility of the host.

### References


American Heart Association, Committee on Standards and Criteria for Programs of Care of the Council of Rheumatic Fever and Congenital Heart Disease. Jones criteria (modified) for guidance in the diagnosis of rheumatic fever. *Circulation* 13: 617–620, 1956.

——, Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease. The evolution of rheumatic heart disease in children. Five-year report of a cooperative clinical trial of ACTH, cortisone, and aspirin. *Circulation* 22: 503–515, 1960.

Feinstein, A. R. Standards, stethoscopes, steroids and statistics. The problem of evaluating treatment in acute rheumatic fever. *Pediatrics* 27: 819–828, 1961.

Feinstein, A. R., and M. Spagnuolo. Experimental reactivation of subsiding rheumatic fever. *J. Clin. Invest.* 40: 1891–1899, 1961.

——. The clinical patterns of acute rheumatic fever: A reappraisal. *Medicine* 41: 279–305, 1962.

Feinstein, A. R., M. Spagnuolo, H. F. Wood, A. Taranta, E. Tursky, and E. Kleinberg. Rheumatic fever in children and adolescents: A long-term epidemiologic study of subsequent prophylaxis, streptococcal infections, and clinical sequelae. VI. Clinical features of streptococcal infections and rheumatic recurrences. *Ann. Int. Med.* 60, Supp. 5: 68–86, 1964a.

Feinstein, A. R., E. K. Stern, and M. Spagnuolo. The prognosis of acute rheumatic fever. *Am. Heart J.* 68: 817–834, 1964b.

Feinstein, A. R., H. Taube, R. Cavalieri, S. G. Schultz, and L. Kryle. Physical activities and rheumatic heart disease in asymptomatic patients. *J. Am. Med. Assoc.* 180: 1028–1031, 1962.

Feinstein, A. R., H. F. Wood, M. Spagnuolo, A. Taranta, S. Jonas, E. Kleinberg, and E. Tursky. Rheumatic fever in children and adolescents: A long-term epidemiologic study of subsequent prophylaxis, streptococcal infections, and clinical sequelae. VII. Cardiac changes and sequelae. *Ann. Internal Med.* 60, Supp. 5: 87–123, 1964c.

Massell, B. F., D. C. Fyler, and S. B. Roy. The clinical picture of rheumatic fever. Diagnosis, immediate prognosis, course, and therapeutic implications. *Am. J. Cardiol.* 1: 436–449, 1958.

Taranta, A., M. Spagnuolo, and A. R. Feinstein. "Chronic" rheumatic fever. *Ann. Internal Med.* 56: 367–388, 1962.

# Radiologic Diagnosis of Congenital Heart Disease in Children*

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Fifteen years ago, a diagnosis of "congenital heart disease" might have been considered adequate. Today, all pediatricians, radiologists, surgeons, and other physicians would insist on more precise anatomic and physiologic information.

The reason for this striking change is shown in table 1. All the lesions listed can be corrected by surgery. They are, then, potentially curable diseases. Almost all of the common congenital heart diseases are in this group. In addition, there are many active programs in clinical research centers searching for satisfactory correction of still other lesions, such as complete transposition of the great vessels (the second most common cyanotic heart disease), Ebstein's anomaly, and single ventricle. Even among those conditions that cannot be cured or corrected, ameliorative procedures are now available. The Blalock operation for tetralogy of Fallot is such a procedure. In this operation, the subclavian artery is used as a shunt vessel to carry blood from the systemic circuit into the pulmonary arterial tree. Another is the Glenn procedure, a superior vena cava-pulmonary artery anastomosis.

Anomalies of the cardiovascular system are a common cause of disease in children. Approximately six of every one thousand live births have some form of congenital heart disease. The prognosis of many of these conditions is very poor. About 90% of infants born with complete transposition of the great vessels succumb within the first year of life. Consequently, early and accurate diagnosis is essential.

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## Classification of Congenital Heart Disease

Classifications based on either anatomic or physiologic pathology are helpful in this regard, and many have been proposed. Because most of the observable clinical abnormalities are reflections of pathologic physiology, the latter approach is more useful.

The simplest classification of this sort is based on the presence or absence of visible cyanosis (table 2A). Patients with desaturated hemoglobin in the peripheral arterial circulation (that is, with right-to-left shunt of blood), as in tetralogy of Fallot or complete transposition of the great vessels, are separated from those with

TABLE 1

Some Cardiac Lesions that can be Corrected

| | |
|---|---|
| Ventricular septal defect | Subvalvular aortic stenosis |
| Atrial septal defect | Tetralogy of Fallot |
| Atrioventricularis communis | The grand trilogy |
| Patent ductus arteriosus | Total anomalous pulmonary venous connection |
| Aortico-pulmonary window | Partial anomalous pulmonary venous connection |
| Coronary artery fistula | Pulmonary valvular stenosis |
| Ruptured sinus of Valsalva | Aortic ring |
| Coarctation of the aorta | Cardiac tumors |
| Aortic stenosis | Congenital ventricular aneurysm |
| Supravalvular aortic stenosis | Congenital mitral stenosis |

TABLE 2

Classifications of Congenital Cardiac Lesions

| A<br>Clinical Classification | B<br>Roentgenologic Classification |
|---|---|
| *Acyanotic* | *Increased pulmonary arterial vasculature* |
| Left to right shunts | Left to right shunts |
| Stenotic lesions: right sided | Admixture lesions |
| left sided | *Normal pulmonary arterial vasculature* |
| Myocardial lesions | Stenotic lesions: left sided |
| Some pulmonary venous obstructive lesions | right sided |
| *Cyanotic* | Myocardial lesions |
| Pulmonary obstruction with right to left shunt | *Decreased pulmonary arterial vasculature* |
| Admixture lesions | Pulmonary obstruction with right to left shunt |
| Some pulmonary venous obstructive lesions | *Increased pulmonary venous vasculature* |
| | Pulmonary venous obstructive lesions |

a left-to-right shunt (such as ventricular septal defect) or those with cardiac conditions without shunt (e.g., coarctation of the aorta).

This classification has inherent disadvantages, however. Many infants and children with conditions characterized by right-to-left shunts have an insufficient quantity of desaturated hemoglobin in the peripheral circulation to be observably blue. About 5 g% of desaturated hemoglobin is required for visible cyanosis, and this is dependent upon a number of factors, such as skin pigmentation. In addition, cyanosis may result from extensive pneumonia, and other pulmonary conditions. For these reasons, a classification (table 2B), based on radiologic observation of the pulmonary blood vessels, was proposed a number of years ago (Lester, Gedgaudas, and Rigler, 1958). This method, too, is based on physiologic considerations. Congenital cardiac conditions are separated into groups dependent upon the pulmonary vascular blood flow.

### Decreased Pulmonary Arterial Vasculature

Patients with a decrease in pulmonary arterial vasculature must have both an obstruction of pulmonary flow (such as pulmonary stenosis or right ventricular infundibular obstruction) and a right-to-left shunt of blood (e.g., through a ventricular septal defect). Tetralogy of Fallot is an example of this, and is defined as infundibular stenosis with ventricular septal defect and right-to-left shunt. Other lesions falling into this group are shown in table 3. Patients with these lesions show arterial $O_2$ desaturation and may be visibly cyanotic. Differential diagnoses within this or other groups may be accomplished by further roentgen observations.

### Increased Pulmonary Arterial Vasculature

Patients showing an increase in pulmonary arterial vasculature fall into one of two sub-groups. By far, the more common is the left-to-right shunt series. These include intracardiac left-to-right shunts, such as ventricular septal defect, and atrial septal defect.

TABLE 3

**Decreased Pulmonary Arterial Vasculature (Cyanotic)**

- Tetralogy of Fallot
- The grand trilogy
- Pulmonary atresia
- "Pseudotruncus arteriosus"
- Tricuspid atresia
- Ebstein's anomaly (with right to left atrial shunt)
- Primary pulmonary hypertension with patent foramen ovale
- Pulmonary arterial hypoplasia or coarctation (may be unilateral)
- Origin of both great vessels from right ventricle with pulmonary stenosis
- Complete transposition of the great vessels with pulmonary stenosis or atresia
- Truncus arteriosus, type IV

Such patients are, of course, fully saturated. In this series, increased pulmonary vasculature is associated with an enlarged, undivided pulmonary artery, and with an aorta that appears normal or somewhat small, and is relatively hypopulsatile. Extracardiac left-to-right shunts include patent ductus arteriosus and aortico-pulmonary window. In these patients, the aorta appears hyperpulsatile and may be enlarged. In addition, extracardiac to intracardiac left-to-right shunts may be seen, such as aneurysm of a sinus of Valsalva with fistula formation and coronary artery fistula (table 4).

In addition, patients with admixture lesions, where both a left-to-right shunt and a right-to-left shunt are essential for maintaining life, usually show increased pulmonary arterial vasculature. In truncus arteriosus, for example, the blood flow from both the left and right ventricles enters a common trunk, from which the flow into the systemic and the pulmonary circulations arises. In complete transposition of the great vessels, too, there is invariably shunting in both directions. These patients are, of course, desaturated, and may be visibly blue. In the admixture group there is frequently (although not always) some degree of malposition of the great vessels. As a result, although the pulmonary arterial vasculature is increased on the roent-

TABLE 4

**Increased Pulmonary Arterial Vasculature (Acyanotic)**

*Left to Right Shunts*

- Ventricular septal defect
- Atrial septal defect
- Atrioventricularis communis
- Left ventricular-right atrial communication
- Patent ductus arteriosus
- Aortico-pulmonary window
- Ruptured sinus of Valsalva
- Coronary artery fistula to right atrium, right ventricle or pulmonary artery
- Partial anomalous pulmonary venous connection
- Lutembacher's syndrome
- Corrected transposition with left to right shunt

TABLE 5

**Increased Pulmonary Arterial Vasculature (Cyanotic)**

*Admixture Lesions*

- Complete transposition of the great vessels
- Origin of both great vessels from right ventricle without pulmonary stenosis
- Other forms of partial transposition of the great vessels
- Truncus arteriosus, types I, II, III
- Single ventricle
- Cor biloculare
- Total anomalous pulmonary venous connection
- Tricuspid atresia with transposition of the great vessels

*Shunt with High Pulmonary Resistance*

- "Eisenmenger complex" and "Eisenmenger physiology"

genograms, the area of the undivided pulmonary artery may appear flat or concave. This is not because the pulmonary artery is small, but rather because it is malpositioned (table 5).

### Normal Pulmonary Vasculature

When the pulmonary arterial vasculature is normal, the lesion is of a variety not associated with shunt mechanisms. Of course, a shunt defect not physiologically significant will also show no abnormality of pulmonary vasculature. These lesions too can be sub-grouped into left-sided ones (coarctation of the aorta), right-sided (isolated pulmonary valvular stenosis), and more generalized ones (Von Gierke's Disease) (table 6).

### Pulmonary Venous Obstruction

In addition, there is a series of relatively rare but important diseases, characterized by pulmonary venous obstruction. These lesions can be recognized by a reticular pattern in the lung fields that represents, not engorged pulmonary arterial vessels, but engorged venous vessels and lymphatics. These patients also may show repeated bouts of pulmonary edema. Such conditions as cor triatriatum and total anomalous pulmonary venous connection to the portal venous system fall into this group (table 7). It should be noted that the more common varieties of total anomalous pulmonary venous connection are admixture lesions, not pulmonary venous obstructive lesions.

### Choice of Radiologic Procedure

Although the status of the pulmonary arterial and venous vasculature is best defined in the frontal roentgenogram, other findings are of particular help in the differential diagnosis of conditions within the major groupings. These include the size and pulsations of the aorta, the pulsations of the pulmonary arterial vessels themselves, the size of the left atrium, and the size of the ventricles. For this reason, the frontal view chest roentgenogram is not a satisfactory examination of the heart. Rather, a series of films and a brief and appropriate fluoroscopic examination are required for full evaluation.

**TABLE 6**

**Normal Pulmonary Arterial Vasculature (Acyanotic)**

| | |
|---|---|
| Coarctation of aorta | Von Gierke's disease |
| Aortic stenosis or insufficiency | Hurler's disease and other metabolic heart disease |
| Aortic ring | Sickle cell disease and other anemias |
| Endocardial fibroelastosis | Congenital ventricular aneurysm |
| Cor triatriatum | Anomalous origin of a coronary artery |
| Pulmonary valvular stenosis | Coronary artery fistula to left side of heart |
| Friedreich's ataxia heart disease | Complete heart block |
| Marfan's disease | Cardiac tumors |
| | Hypertensive heart disease |

**TABLE 7**

**Increased Pulmonary Venous Vasculature**

- Stenosis or atresia of pulmonary veins
- Cor triatriatum
- Mitral atresia
- Mitral stenosis
- Anomalous pulmonary venous connection, through stenotic channels
- Anomalous pulmonary venous connection to the portal venous system
- Aortic atresia
- Severe aortic stenosis
- Severe coarctation of the aorta
- Complete interruption of the aortic arch

**TABLE 8**

**Initial Cardiac Films**

(All Films at 6 Foot Target-Film Distance—Upright)

- Postero-anterior*
- Lateral*
- Right anterior oblique, 45°*
- Left anterior oblique, 60°

* Thick barium in esophagus.

*Additional Films*

- Supine antero-posterior at 30 inch distance—for left atrium
- Roentgen kymograms—for valve calcification, pulsations
- Cinefluorographic strips—for pulsations, calcifications
- Planigrams—for valve calcification

The routine cardiac films most suitable for differential diagnosis are listed in table 8.

The status of fluoroscopic examination has been brought into question in recent years. This is a result of misunderstanding the use of the fluoroscope in these conditions. It is feckless to use the fluoroscopic examination for evaluating factors which can be determined better from the roentgenograms. On the other hand, dynamic characteristics, such as the pulsations of the undivided pulmonary artery and its major branches and the pulsations of the aorta, can be evaluated only by fluoroscopy. For this purpose, image intensification fluoroscopy, rather than a conventional fluoroscope, is essential.

### Evaluation of Radiographic and Fluoroscopic Findings

An order of significance of radiographic and fluoroscopic findings can be derived. Some features, such as the status of the pulmonary arterial vasculature, are well evaluated radiographically and are consequently of great significance. Others, such as chamber enlargement with the exception of left atrial enlargement, are poorly evaluated radiographically and other methods are more satisfactory. An order of significance is indicated in table 9.

Utilizing simple roentgen methods (radiographic films and image intensification fluoroscopy) in association with the other simple diagnostic methods (physical examination, history, and

electrocardiography), a firm clinical diagnosis can be established in more than 85% of the patients. However, further information is usually needed. A decision to attempt surgical correction depends upon precise knowledge of the physiologic effect of the anatomic defect. For example, a patient with ventricular septal defect, having only a modest increase in pulmonary arterial pressure, represents an excellent surgical risk. Appropriate repair should result in complete correction of the condition. On the other hand, a patient having very high pulmonary resistance may be a poor risk, and surgery may be contra-indicated. This sort of data is best established by cardiac catheterization.

### Selective Angiocardiography

Surgical correction also is dependent upon a knowledge of the precise anatomic pathology. In tetralogy of Fallot, for example, the degree of infundibular obstruction, the length of the hypertrophied crista supraventricularis, the size of the ventricular septal defect, the degree of pulmonary valvular obstruction, and the degree of overriding of the aorta are all of great importance. This sort of precise anatomic information requires selective angiocardiography.

Generally, venous angiocardiography (injection of a bolus of contrast material into a peripheral vein with filming of the heart) is unsatisfactory because of overlapping structures and a poor concentration of contrast material at the point of interest. Selective study, with a catheter placed in relation to the expected area of maximum importance, is much superior and should replace the cruder methods. In order to accomplish this, the conventional studies must be used in order to determine what information is to be obtained. Right-sided selective angiocardiography is most satisfactory in a large variety of conditions. These include tetralogy of Fallot and pulmonary stenosis (table 10). Injection into the left side of the heart is required in others (table 11). In extracardiac conditions involving the aorta, selective injection above the aortic valve, or other locations within the aorta, may be necessary (table 12).

**TABLE 9**

**Radiographic and Fluoroscopic Findings in Order of Significance**

- Pulmonary arterial vasculature
  - a. Normal, increased or decreased on radiographs
  - b. Degree and character of pulsations at fluoroscopy
- Pulmonary venous vasculature and pulmonary lymphatics
- Size and pulsations of undivided pulmonary artery
- Size and pulsations of aorta
- Heart size
- Chamber enlargement
  - a. Left atrium
  - b. Right ventricle
  - c. Left ventricle
  - d. Right atrium

**TABLE 10**

**Some Indications for Right Sided Angiocardiography**

- Congenital heart disease with decreased pulmonary arterial vasculature
- Congenital heart disease with increased pulmonary arterial vasculature
  - a. Admixture lesions
  - b. Bidirectional shunt
- Anatomic definition of pulmonary valvular and/or infundibular stenosis
- Anomalies of the pulmonary vascular tree
- Inability to enter the pulmonary artery at cardiac catheterization
- Congenital heart disease with increased pulmonary venous vasculature
- Differential diagnosis between cardiac dilatation and pericardial effusion
- Cardiac tumors
- Certain pericardiac tumors

**TABLE 11**

**Some Indications for Left Sided Angiocardiography**

- Evaluation of mitral competance in acquired heart disease
- Evaluation of mitral competance following surgery for mitral disease
- Subvalvular aortic stenosis
- Small intracardiac and extracardiac left to right shunts with questionable findings at right heart catheterization; anatomic definition of such lesions
- Balanced septal defects
- Patent ductus arteriosus associated with pulmonary insufficiency or with ventricular septal defect
- Certain admixture lesions
- Evaluation of left side of heart in complex congenital anomalies

**TABLE 12**

**Some Indications for Thoracic Aortography**

- Coarctation of the aorta
- Patent ductus arteriosus
- Aortico-pulmonary window
- Coronary artery fistula
- Anomalous coronary artery
- Ruptured sinus of Valsalva
- Aortic stenosis and/or insufficiency
- Supravalvular aortic stenosis
- Aortic ring
- Aneurysm of the aorta

## Summary

1. The importance of precise anatomic and physiologic diagnosis in congenital heart disease has been emphasized in recent years, because of the increasing possibilities of surgical correction.

2. The x-ray examination is a powerful tool in the evaluation of patients with congenital heart disease. A method of evaluation is presented, using conventional roentgenographic and fluoroscopic examination along with other simple clinical methods. This approach is relatively simple, can be carried out as an office procedure, and yields a firm clinical diagnosis in the majority of cases.

3. Cardiac catheterization and selective angiocardiography may be necessary to give precise information on physiological abnormalities and anatomic defects. These techniques require expensive equipment and a team of physicians.

4. The challenge of accurate diagnosis in these common anomalies is great. The potential reward, in terms of restoring a normal life span, is also great. An aggressive approach to a correct diagnosis is urged.

## Reference

LESTER, R. G., E. GEDGAUDAS, AND L. G. RIGLER. Method of radiologic diagnosis of congenital heart disease in children. *J. Am. Med. Assoc.* 166: 439–443, 1958.

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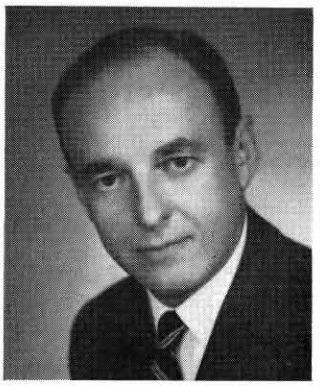

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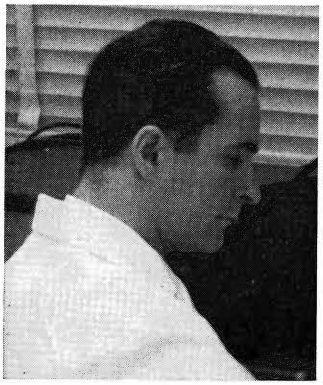

**Walter J. Geeraets** (*Laser in Clinical Ophthalmology*), director of ophthalmic research and professor of ophthalmology at the Medical College of Virginia, was born in M. Gladbach, Germany. He obtained a doctor's degree in medicine, with a thesis on leukemia in children, from the University of Bonn. He later served as a research fellow at the Radiation Institute of that university and as the chief assistant of the surgical clinics at Bochum, Germany. He came to the Medical College of Virginia in 1957 with appointments in the departments of ophthalmology and biophysics.

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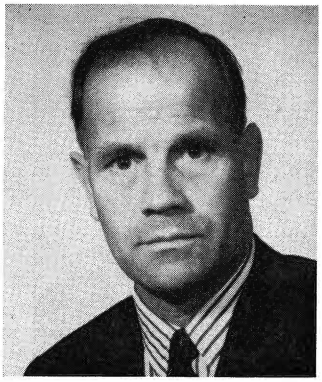

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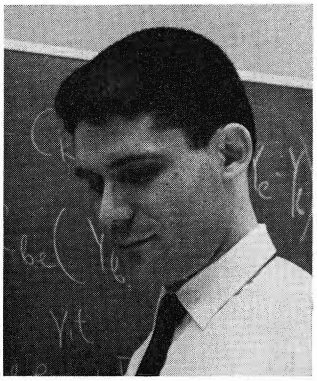

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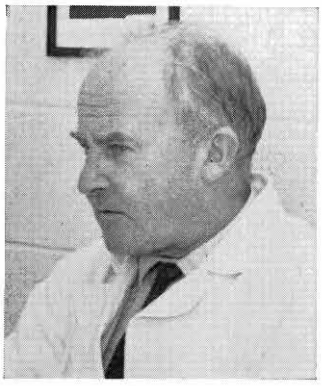
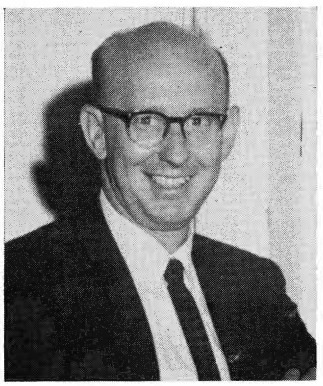
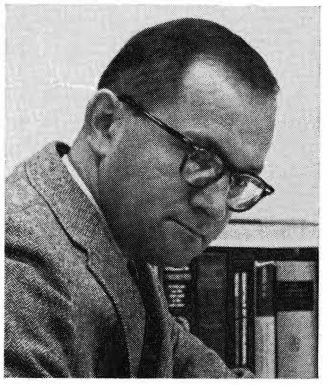


**Sir George White Pickering** (*What is a Modern Physician?*), Regius professor of medicine at Oxford University since 1956, was the McGuire Lecturer at the Medical College of Virginia in 1964. From 1939 to 1956 he was professor of medicine at the University of London, and director of the medical clinic of St. Mary's Hospital in London. Professor Pickering was educated at Dulwich and Pembroke Colleges of Cambridge University. He is a member of the Association of American Physicians and a Fellow of the Royal Society; he served as president of the British Medical Association from 1963 to 1964. In the fall of 1964, he spent one week at the Medical College of Virginia as a visiting professor in the department of medicine.

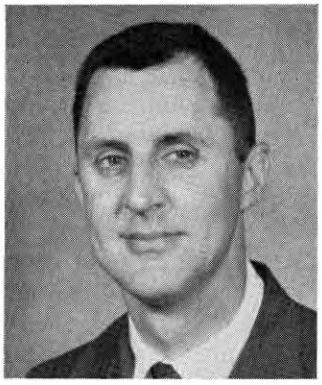


**David W. Richardson** (*Central Nervous Control of Blood Pressure in Man*) is associate professor of medicine and occupant of the Virginia Heart Association chair of cardiovascular research at the Medical College of Virginia. After receiving his M.D. from Harvard, he interned and started his medical residency at Yale. He completed his clinical and research training at M.C.V. From 1956 to 1961 he was chief of the cardiovascular section and associate chief of staff for research at the Richmond V.A. Hospital. He has remained in Richmond except for the academic year 1962–1963, which he spent as a visiting fellow in the research laboratories of Sir George Pickering, at the University of Oxford, England.



**Edwin F. Rosinski** (*An Approach to Medical Education: The Medical College of Virginia School of Medicine Curriculum*) is professor of medical education and director of research in medical education at M.C.V. He is a consultant on medical education for the medical and natural sciences division of the Rockefeller Foundation. Dr. Rosinski came to M.C.V. in 1959 from the University of Buffalo School of Medicine where he had directed research for Project in Medical Education. He also received his Ed.D. degree and served as senior research associate at that university.

**Ralph M. Scott** (*Place of Radiotherapy in the Management of Oral Cancer*) is professor of radiology and director of radiation therapy at the University of Louisville School of Medicine. Before moving to Kentucky, he was in charge of radiation therapy and nuclear medicine at the Robert Packer Hospital and Guthrie Clinic in Sayre, Pa., and later assistant professor of radiology at the University of Chicago School of Medicine. Dr. Scott was born in Leemont, Va., received his B.A. from the University of Virginia, and his M.D. at the Medical College of Virginia. Part of his earlier training in radiation therapy was during a fellowship at the Christie Hospital and Holt Institute in Manchester, England.



**Malcolm E. Turner** (*Physiological Basis of the Radioisotope Renogram*) is professor and chairman of the department of biometry at Emory University. Before going there he was chairman of the division of biometry, department of biophysics, at the Medical College of Virginia. Dr. Turner received his Ph.D. degree from North Carolina State College. He has held teaching positions at the University of Cincinnati College of Medicine and at North Carolina State College. He is currently managing editor of *Biometrics*.

**Alton R. Sharpe, Jr.** (*Physiological Basis of the Radioisotope Renogram*) is associate professor of nuclear medicine at the Medical College of Virginia. He earned his B.S. degree at the University of Richmond and his M.D. degree at the Medical College of Virginia, and later did his internship and residency at M. C. V. He has served as chief of the radioisotope laboratory, associate chief of staff for research, and consultant in nuclear medicine at the McGuire V. A. Hospital in Richmond.

Panelists at the McGuire Symposium, 1964. From left, Sir George Pickering, Drs. Harold W. Schnaper (chief, research in Internal Medicine, V.A. Central Office, Washington, D.C.), William Hollander, William Dock, Jeremiah Stamler, William R. Harlan, Jr., and Lyman A. Fisher.

**MEDICAL COLLEGE OF VIRGINIA/FALL 1965**

SEPTEMBER 20–24, 1965

AMERICAN COLLEGE OF PHYSICIANS COURSE ON BASIC MECHANISMS IN INTERNAL MEDICINE

A five-day course, open to all interested physicians, to be held in the Porter Auditorium, Medical Education Building, September 20–24, 1965.

MONDAY—SEPTEMBER 20
A.M.

8:00 *Registration*
8:45 *Welcome*—Dr. Kinloch Nelson, Dean, School of Medicine, co-director. Dr. Charles M. Caravati, department of medicine, MCV, and vice-president, American College of Physicians, co-director. Dr. W. T. Thompson, Jr., chairman, department of medicine, MCV, director.

GASTROENTEROLOGY

9:00 *Changing Patterns of Pancreatitis*—Dr. Benjamin B. Weisiger, McGuire V. A. Hospital, Richmond, Va.
9:25 *Interrelationships between Malabsorption and Maldigestion Syndromes*—Dr. John T. Farrar, department of medicine, MCV.
10:15 Intermission
10:25 *Cholestatic Jaundice*—Dr. Fenton Schaffner, department of pathology, Mount Sinai Hospital, New York, N. Y.
11:10 *Achalasia, Diffuse Esophageal Spasm and Related Disorders*—Dr. Alvin M. Zfass, department of medicine, MCV.
11:30 *Panel: "Pearl Diving"*—Drs. Caravati, Farrar, Schaffner, Weisiger, and Zfass.

P.M.

RENAL—SALT AND WATER

1:30 *Current Concepts of Renal Physiology; Clinical Evaluation*—Dr. Newton C. Brackett, department of medicine, MCV.
2:00 *Renal Tubular Function; Syndromes of Altered Function*—Dr. T. Franklin Williams, University of North Carolina School of Medicine.
2:30 *Disturbances of Acid-Base Equilibrium*—Dr. Brackett.
3:30 Intermission
3:45 *Nephrosis; Diagnosis and Management*—Dr. Russell Randall, department of medicine, MCV.
4:15 *Acute Renal Failure; Diagnosis and Management*—Dr. I. Norman Sporn, department of medicine, MCV.
4:45 *Chronic Renal Failure; Methods of Management;* Renal Transplant—Dr. John Setter, department of medicine, MCV.

TUESDAY—SEPTEMBER 21
A.M.

NEUROLOGY

8:30 *Clinical Syndromes and Diagnostic Procedures in "Stroke"*—Dr. Laurie E. Rennie, division of neurology, department of medicine, MCV.
9:15 *Use of Echoencephalogram in Neurological Diagnosis*—Dr. Mitchell J. Dreese, associate professor, division of neurology, department of medicine, MCV.
9:30 *Chronic Meningitis; Diagnosis and Treatment (Emphasis on Fungus Infection)*
10:15 Intermission
10:30 *Diagnosis of Muscular Weakness*—Dr. Cary G. Suter, chairman, division of neurology, department of medicine, MCV.
11:15 *Muscle Biopsy for Diagnosis of Muscle Disease*—Dr. Julio Garcia, department of pathology, MCV.
11:30 *Chemical Tests in the Diagnosis of Neurological Disease*—Dr. Nicholas Papadopoulos, Walter Reed Army Institute of Research, Washington, D. C.

P.M.

HEMATOLOGY

1:30 *The Peripheral Blood Smear, Its Value in Diagnosis*—Dr. G. Watson James, III, department of medicine, MCV.
2:00 *Critique of Recent Advances in Hematology*—Dr. Oscar O. Thorup, department of medicine, MCV.
2:45 *Uncommon Hemolytic Anemia and Red Cell Enzyme Systems*—Dr. John Moon, department of medicine, MCV.
3:05 Intermission
3:20 *Chronic Granulocytic Leukemia, Its Variants and Clinical Variability*—Dr. Waldo Scott, Newport News, Va.
3:40 *Understanding Coagulation Disorders*—Dr. Lyman Fisher, division of clinical pathology, department of pathology, MCV.
4:10 *Differential Diagnosis of Vitamin $B_{12}$ and Folic Acid-Deficiency Anemia*—Dr. William T. Dabney, III, department of medicine, MCV.
4:35 *The Thymus, Lymphoreticular Disease and γ-Globulin Abnormalities*—Dr. James.
7:00 to 9:00 Faculty "open offices and laboratories"—Medical Education Building; Elective seminars and group discussions.

WEDNESDAY—SEPTEMBER 22
A.M.

CARDIOVASCULAR-PULMONARY

8:30 *Basic Physiology; Cardiac Catheterization in the Evaluation of Acquired Valvular Disease*—Dr. V. E. Kemp, department of medicine, MCV.
9:15 *Application of Catheterization to Diagnosis of Common Congenital Heart Disease*—Dr. H. Page Mauck, department of medicine, MCV.

9:45 Intermission
11:30 *Arrhythmias and Cardioversion*—Dr. Alston Blount, Richmond, Va.

P.M.

1:30 *Pulmonary Physiology for the Clinician*—Dr. Thompson.
2:00 *Considerations and Applications of Hyperbaric Oxygenation*—Dr. Herbert O. Sieker, department of medicine, Duke University School of Medicine.
2:45 Intermission
3:00 *Panel Discussion on Emphysema; etiology, pathophysiology, and treatment*—Moderator, Dr. John L. Patterson, Jr., department of medicine, MCV. Co-panelists, Dr. Edward S. Ray, department of medicine, MCV; Drs. Sieker and Thompson.
4:00 *Treatment of Bacterial Pneumonias (Emphasis on New Agents)*—Dr. Utz.
4:30 *Asbestosis and Pulmonary Malignancies*—Dr. Harry I. Lurie, department of pathology, MCV.
4:45 *Alveolar Proteinosis*—Dr. C. F. Wingo, V. A. Hospital, Richmond, Va.

THURSDAY—SEPTEMBER 23
A.M.

CARDIOVASCULAR-PULMONARY, cont.

8:30 *Control of Blood Pressure*—Dr. Eugene Stead, chairman, department of medicine, Duke University School of Medicine.
9:15 *Efficacy of Drug Treatment of Hypertension*—Dr. David W. Richardson, department of medicine, MCV.
9:30 Panel: *Diagnosis of Surgically Curable Hypertension and Efficacy of Therapy*—Moderator, Dr. Richardson. Co-panelists, Dr. Hume, chairman, department of surgery, MCV; Dr. Charles O. Watlington, department of medicine, and Dr. Stead.
10:00 Intermission
10:15 (Panel continued)
10:45 Panel: *Coronary Disease*—Moderator, Dr. Kemp. Co-panelists: Dr. William H. Sewell, V.A. Hospital, Oteen, N. C.; Dr. John W. Jones, department of medicine, McGuire V.A. Hospital.
11:30 *Digitalis*—Dr. Eugene Braunwald, chief, Cardiology Branch, National Heart Institute, National Institute of Health, Bethesda, Md.

P.M.

CONNECTIVE TISSUE

1:30 *Plasma Proteins in Health and Disease*—Dr. P. Franklin Mullinax—department of medicine, MCV.
2:00 *Significance of the Serologic Reactions of the Rheumatoid Factors*—Dr. Marion Waller, department of medicine, MCV.
2:30 *Synovial Reaction in Rheumatoid Arthritis, Gout, and Pseudogout*—Dr. Daniel J. McCarty, Hahneman Medical Center, Philadelphia, Pa.
3:00 Intermission
3:15 *Current Concepts of Pathogenesis and Treatment of Gout*—Dr. W. Robert Irby, department of medicine, MCV.
3:45 *Systemic Manifestations of Rheumatoid Arthritis*—Dr. John Kelly, chief, medical service, McGuire V.A. Hospital.
4:15 *Problems of Treatment of Rheumatoid Arthritis*—Dr. Elam C. Toone, Jr., department of medicine, MCV.
4:45 *Summation*
7:00 to 9:00 Faculty "open offices and laboratories"—Medical Education Building; Elective seminars and group discussions.

FRIDAY—SEPTEMBER 24
A.M.

ENDOCRINOLOGY AND METABOLISM

8:30 *Advances in Endocrinology*—
*The Thyroid*—Dr. Richard N. Kirkland, department of medicine, MCV.
*The Adrenals*—Dr. Herhchel L. Estep, department of medicine, MCV.
*The Parathyroids*—Dr. John R. Handy, department of medicine, McGuire V.A. Hospital.
9:30 *Principles of Lipid Metabolism*—Dr. William R. Harlan, Jr., director, Clinical Research Center, MCV.
10.00 Intermission
10:15 *Disorders of Lipid Metabolism*—Dr. Harlan.
10:45 *What is Diabetes*—Dr. H. St. George Tucker, Jr., department of medicine, MCV.
11:15 *Chromosomal Disorders*—Dr. Ruben B. Young, department of pediatrics, MCV.
11:45 *Newer Isotope Scanning Procedures*—Dr. Alton R. Sharpe, Jr., department of radiology, MCV.

P.M.

DERMATOLOGY

1:30 *Dermal Elastoses;* Biochemical and Clinical Manifestations—Dr. J. Doyle Smith, chairman, department of chemistry and pharmaceutical chemistry, school of pharmacy, MCV.
2:30 *Metabolic Abnormalities Reflected in the Skin and Mucous Membranes*—Dr. Robert Scoggins, division of dermatology, department of medicine, MCV.
3:00 Intermission
3:15 *Cutaneous Manifestations of the Collagen Vascular Diseases*—Dr. Allen Pepple, chairman, division of dermatology, department of medicine, MCV.
3:45 *Dermatologic Clues to Internal Malignancies*—Dr. Kenneth W. Blaylock, division of dermatology, department of medicine, MCV.
4:15 *The Sweat Gland in Health and Disease*—Dr. Gary W. Cage, National Cancer Institute, National Institute of Health, Bethesda, Maryland.

TUITION

$60 for members of the College, $100 for non-members.
For further information and registration, contact Dr. Edward C. Rosenow, Jr., executive director, American College of Physicians, 4200 Pine Street, Philadelphia, Pa., or Dr. W. T. Thompson, Jr., chairman, department of medicine, MCV.

# MCV/Q

**MEDICAL COLLEGE OF VIRGINIA QUARTERLY**

*A Scientific Publication of the School of Medicine*

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