CLINICAL PROGRESS

Isotope Technics in Clinical Cardiology

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THIS REVIEW is an attempt to answer two questions. First, are there any isotope technics available at the present time that are really useful in the care of patients? And second, what will be the role of isotope technics in clinical cardiology a few years from now?

Historical Review

The use of isotopes in clinical cardiology was introduced by Blumgart, Yens, and Weiss, who used radium C and a cloud chamber to estimate the linear velocity of blood flow in an extensive series of studies starting in 1927.[1, 2] Undoubtedly the major stimulus to the adoption of tracer technics came from the introduction of man-made radioisotopes after World War II. During the immediate postwar period several new methods were described. Quimby and Smith[3] and Kety[4] introduced the use of isotope clearance as a method of measuring the rate of blood flow to tissues. Prinzmetal and his collaborators used a Geiger counter placed over the precordium to follow the circulation of a bolus of radioactive blood through the right and left sides of the heart. They dubbed this procedure "radiocardiography."[5] In 1953, Waser and Hunzinger made the first attempts to measure coronary blood flow by labeling the coronary blood with an isotope.[6] Although the first of these technics was introduced almost 40 years ago, the practical application of isotope technology to clinical problems has been slow. There have been a number of reasons for the lag. The crude nature of the counters and radioactive tracers that have been available until recently is probably the most important factor. The requirement of a special federal license to use isotopes has undoubtedly been a deterrent. Recently steps have been initiated to make isotopes available to all physicians without special approval. This is an important step in the right direction.

Radiocardiography

Several of the successfully developed methods have not been used by clinicians in the care of patients. For instance, from the radiocardiogram it is possible to determine cardiac output,[7–9] the amount of blood in the lungs,[10, 11] and the relative amounts of blood in the right and left sides of the heart.[12] A single injection of I^{131} albumin and the use of inexpensive counting equipment are all that is needed. Serial measurements of cardiac output or pulmonary and intracardiac blood volumes might be helpful in some clinical situations, but to date cardiologists have relied on a history of the patient's illness and a physical examination or x-ray to make an estimate of these functions, rather than calling for actual measurements.

Intracardiac Blood Volume

The most useful isotope technic at present is the heart scan.[13] The circulating blood can be effectively labeled by a single intravenous

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injection of I^{131} albumin, and the intracardiac blood pool then outlined with use of a commercial scanning apparatus designed for thyroid studies. The usual clinical question is to determine whether a large heart shadow is caused by dilatation of the heart or by pericardial effusion. When cardiac dilatation is present, almost the entire area corresponding to the heart shadow is radioactive. In pericardial effusion, the blood pool is normal in size, even though the heart shadow is enlarged. At present, the interpretation of cardiac scans is in part subjective, and errors arise due to variations in the technic used in producing the visual record. Cardiac scanning should be made a more objective and quantitative method. One approach has been to estimate the actual volume of blood within the heart from the total counting rate over the precordium.[12] Patients with pericardial effusion have much less intracardiac blood for the same size of heart shadow than normal subjects or those with other forms of heart disease. This technic is also sensitive to the presence of myocardial hypertrophy. With technical advances, it should be possible to measure the amount of blood within the heart rather precisely. A more accurate outline of the blood pool would be useful in detecting aneurysms of the ventricles, pericardial cysts, and loculated pericardial effusion. There is no reason why the myocardium cannot be tagged with a different isotope and its location outlined in the same way.

Pulmonary Embolism

Scans of the lung have been used in an attempt to improve the diagnosis of pulmonary embolism. The lung is outlined by injecting fine particles of labeled, precipitated albumin.[14] These particles form micro-emboli which lodge in the pulmonary capillaries and therefore outline the pattern of blood flow to the lung. Since only a few milligrams of protein are injected, the emboli produce no physiologic effects. In the presence of pulmonary embolism, there is a nonradioactive zone corresponding to the unperfused area of the lung.[15] This technic has not been in use long enough for a reliable evaluation. The main limitation seems to be that most of the lesions commonly confused with pulmonary infarction also give a negative shadow on the scan. This includes bronchopneumonia. This technic is probably best suited for cases of suspected embolization in which no change can be made out in the routine radiogram. However, lung cysts and sequestration of the lung can produce a picture on the scan similar to that in pulmonary embolism.

Coronary Blood Flow

The rate of coronary blood flow in man has been estimated in three ways: (1) by measuring how fast an isotope which is injected into the blood is taken up by the myocardium; (2) by following a bolus of tagged blood as it flows through the coronary vessels; and (3) by measuring the rate at which a freely diffusible inert gas is washed out of the heart muscle by the blood.

Several studies have used uptake of rubidium from the blood as an index of coronary flow. Rubidium is biologically similar to potassium. When Rb^{86} is infused intravenously, 50 to 90 per cent of the isotope in coronary arterial blood crosses the capillaries and enters the cells. The rate of coronary blood flow and the amount of isotope taken up are closely related.[16] In one study in dogs the mean error in estimating the rate of coronary blood flow from the rate of Rb^{86} clearance was approximately 8 per cent.[17] To estimate myocardial Rb^{86} uptake in man a precordial counter has been switched back and forth between the precordium and the upper sternum.[18] It was assumed that the difference between these two areas was a measure of the amount of radioactivity actually in the heart. With this data, plus a second determination of radioactivity 24 hours later, it was possible to estimate rates of coronary blood flow. A small group of patients with severe coronary artery disease had low or low normal flow values. This group also had reduced cardiac output. Recently this procedure has been modernized by substituting Rb^{84} for Rb^{86}.[19] Rb^{84} is a positron-emitting isotope. Therefore it is possible to eliminate heavy shielding, and to limit the zone monitored to the cylinder of

tissue that lies between a pair of scintillation crystals. One pair is placed over the heart. The other is put over the right chest to estimate the contribution of the chest wall to the count recorded by the pair over the heart. The difference in counting rates over the heart and the right chest divided by the radioactivity of the arterial blood gives an index of Rb^{84} clearance. Although the effect of some maneuver, such as administration of nitroglycerin, on this "clearance equivalent" can be estimated in this way, some measure of the amount of myocardium being monitored is needed if clearance rates in one patient are to be compared with those in another.

Sapirstein introduced a different method of using isotope uptake by the myocardium to determine the rate of blood flow.[20] Single injections of K^{42} or Rb^{86} were given intravenously to animals, and the fraction of the total amount of isotope taken up by the heart muscle was then measured after removing the heart. This fraction is believed to be the same as the fraction of the cardiac output that goes to the myocardium. Recently this approach has been applied to man by an external monitoring technic.[21] This method yields reasonable answers. However, after a single intravenous injection, the concentration of isotope in the blood is changing rapidly. The dynamics of the isotope within the heart during this time and the parallel behavior of total cardiac radioactivity have never been worked out in detail. Therefore the main assumption of this approach is still not adequately supported by data.

The most appealing aspect of the methods based on measuring uptake of an isotope from the blood is the fact that it may be possible to obtain an actual picture or map of the differences in the rates of blood flow to different parts of the heart by this approach.[22–25] The methods that use intravenous tracers to tag the myocardium have several limitations in common. One problem is that the isotope is also taken up by the tissues adjacent to the heart, and not by the myocardium alone. All tracers are to some extent involved in metabolic processes. Therefore the relationship of blood flow and isotope clearance varies somewhat from subject to subject. Another problem is that, at present, there is no accurate way of quantitating the absolute amount of isotope in the heart by using an external monitor. In the case of Rb^{84}, the isotope itself is expensive. However the attractive features of these methods justify continued efforts to improve the technics.

A second main approach to measuring coronary blood flow in man is based on the idea that the circulation of radioactive blood within the coronary vessels can be identified in the descending limb of the left ventricular portion of the radiocardiogram. This contribution has been seen as a discrete peak,[26] a less well defined superposition on the left ventricular segment,[27] and as a difference between the slope of the left ventricular segment and that of a simultaneous arterial curve.[28] There is no denying that the circulation of blood within the coronary arteries must influence the radiocardiogram to some extent, but attempts to quantitate coronary blood flow in this way have seemed fanciful to some,[29–31] if not most, of the workers in this field.

The development of methods for catheterizing the left ventricle and coronary arteries has lead to expansion and modification of technics for measuring coronary blood flow with radioactive gases. In one of the methods being used at present a solution containing krypton-85 is injected through a catheter which has been passed into the left ventricle.[32] Approximately 5 per cent of the krypton enters the coronary circulation and much of this lodges in the myocardium. Blood samples are taken from a catheter in the coronary sinus and their radioactivity is plotted against time. By making the same assumptions used in the nitrous oxide technic of Kety and Schmidt,[33] it is possible to calculate the rate of coronary blood flow. The radioactivity is used only to simplify measurements of blood gas content. External monitoring is not done. The concentration of krypton in arterial blood is not taken into account in making calculations of flow rate and the venous concentration curves are analyzed as if they were single expo-

nential functions. In a second method for making the same type of measurement, the tip of a catheter is placed in one of the coronary arteries and a solution of krypton-85 or xenon-133 is injected directly into the artery.[34] During the first circulation of the tracer, most of the gas enters the myocardium and any other tissues which are supplied by the coronary artery. As soon as the tracer has been cleared from the arterial blood, it begins to diffuse back into the blood flowing through the myocardium. The fall in precordial radioactivity is followed with an external monitor. In this method, 60 to 80 per cent of the myocardial radioactivity has been found to disappear as a single exponential function.[34] In the form described, this technic gives values for coronary flow which are lower than those with the nitrous oxide technic.[35] The slower components of these curves might be caused by areas with reduced coronary blood, by blood flowing to epicardial fat, by direct diffusion of gas out of the heart, or by interference from radioactivity in the chest wall, blood, or lungs. These slow components could be analyzed by established mathematical technics.[36] Xenon-133 has gamma rays with very low energy. Therefore the sternum, ribs, and chest wall will absorb significantly different portions of the radiation originating in the heart. Consequently some parts of the tagged area of myocardium will have a greater representation in the precordial counts than others. These methods measure flow in volume of blood per 100 Gm. of myocardium which is actually perfused to a detectable extent during the period of study. Therefore muscle with very slow rates of blood flow will not be detected. The nitrous oxide method[33] requires that the myocardium be saturated with the tracer. However, in the technics that rely on a single circulation of the tracer to tag the myocardium it is probable that areas with slow flow receive less of the radioactive gas, and therefore make a proportionately decreased contribution to the wash-out curve.[37] Catheterization of a coronary artery is of course a more ambitious maneuver than catheterization of the coronary sinus, but if the subject is already having the procedure done in order to make arteriograms, there is presumably no additional hazard from the measurements of coronary flow rate. With direct injections into the coronary arteries, some control can be exercised over the part of the heart studied, and recirculation of tracer is almost eliminated.

None of the methods of measuring coronary flow has been shown to be useful in the care of patients. To find a clinical role, a technic should make an earlier diagnosis of coronary artery disease, or perhaps outline the extent of the obstruction to blood flow, or make it possible to follow the effect of therapy on coronary blood flow. To achieve these goals, any method will probably need to give the comparative rates of blood flow in the areas supplied by the major coronary arteries. Coronary blood flow is apparently not greatly reduced in most people with coronary artery disease when they are at rest.[38] For this reason, to detect coronary narrowing by measuring blood flow it will be necessary to measure the response of the coronary vascular bed to a stress such as exercise.

Instrumentation

Many of the defects of present methods may be eliminated by improvement of the instruments and isotopes used. One direction of change is the increase in the size of NaI scintillation crystals usually employed to detect the radiation. At one time a single crystal 1-inch wide and 1-inch long was considered adequate. Now a pair of crystals eight times as wide and three times as thick is not thought to be unreasonable. The large size is important because, with the same radiation load to the patient, almost 400 times as many counts can be picked up with the larger crystals. An increase in counting rate brings better counting statistics, which in turn means that the focusing collimation can be more selective, making it possible to come closer to counting only the isotope which is in the area of interest. Unfortunately a big crystal requires a big shield. Some of these now weigh over 1,000 lb. A scanner can be programmed to move in several different patterns to obtain the same focus-

ing effects that are present in x-ray planography.[39] The data from scanning studies are frequently obtained in a form that is difficult for the operator to interpret. At least a half dozen ways of presenting the data have been used. These include scans in color,[40] and automatic processing for presentation on a TV monitor.[41] Another approach is to have the data processed by a computer to give an isocount contour map.[42] These are basically the same as the familiar geodetic survey maps. Another direction of technical development is represented by the scintillation camera and auto-fluoroscope.[43, 44] Each time a gamma ray is absorbed in the scintillation crystal a flash of light is given off. By using a series of phototubes and the appropriate electronic circuits it is possible to determine the location of the flashes and to reproduce a picture of the distribution of the isotope within the body. The possibility of making moving pictures is obvious.

The present philosophy is to use quantities of tracer that deliver an insignificant dose of radiation. The amount of useful information obtained from a study is usually increased by raising the dose of the isotope. One method of increasing the isotope dose safely is to use an isotope that decays rapidly. In some centers isotopes with physical half-lives of only a few minutes are available from cyclotrons. In other laboratories short-lived isotopes are being milked from "cows." An isotope cow consists of a container holding a supply of one isotope which, in the process of decaying, gives rise to a daughter isotope. In one case germanium-68, which has a half-life of 280 days, gives rise to gallium-68, with a half-life of 68 minutes.[45] The gallium is "milked" from the germanium, giving rise to the term cow. Another approach to reduce the radiation received is to attach the tracer to a rapidly excreted substance such as iodipamide.[46]

Summary

Scans of the cardiac blood pool are of practical value and are being widely used. Simple methods of measuring cardiac output and blood volume are available, but they have not yet been exploited by clinicians. With the rapid advances in nuclear technology, practical and innocuous methods for measuring regional blood flow in the heart and other areas will probably become available in the near future. Such methods will undoubtedly be used by clinical investigators. Their widespread clinical application will depend on whether or not they provide a practical way of solving a recognized medical problem.

References

1. BLUMGART, H. L., AND YENS, O. C.: Studies on the velocity of blood flow: I. The method utilized. J. Clin. Invest. **4**: 1, 1927.
2. BLUMGART, H. L., AND WEISS, S.: Studies on the velocity of blood flow: II. The velocity of blood flow in normal resting individuals, and a critique of the method used. J. Clin. Invest. **4**: 15, 1927.
3. QUIMBY, E. H., AND SMITH, B. C.: Tracer studies with radioactive sodium in patients with peripheral vascular disease (preliminary report). Science **100**: 175, 1944.
4. KETY, S. S.: Quantitative measurement of regional circulation by the clearance of radioactive sodium. Am. J. M. Sc. **215**: 352, 1948.
5. PRINZMETAL, M., CORDAY, E., SPRITZLER, R. J., AND FLIEG, W.: Radiocardiography and its clinical applications. J.A.M.A. **139**: 617, 1949.
6. WASER, P., AND HUNZINGER, W.: Radiocirculographische Untersuchung des Coronarkreislaufes mit $Na^{24}Cl$. Cardiologia **22**: 65, 1953.
7. HUFF, R. L., FELLER, D. D., AND BOGARDUS, G.: Cardiac output by body surface counting of I^{131} human serum albumin. J. Clin. Invest. **33**: 944, 1954.
8. VEAL, N., PEARSON, J. D., HANLEY, T., AND LOWE, A. E.: A method for determination of cardiac output (preliminary report). Proceedings of second isotope conference, London. Butterworth Scientific Publ. 1954, p. 183.
9. MACINTYRE, W. J., PRITCHARD, W. H., AND MOIR, T. W.: The determination of cardiac output by the dilution method without arterial sampling: I. Analytical concepts. Circulation **18**: 1139, 1958.
10. LAMMERANT, J., AND DEVISSCHER, M.: The determination of mean pulmonary circulation time and pulmonary circulating blood volume in man with iodinated (I^{131}) human serum albumin. Strahlentherapie **36**: 128, 1956.
11. DONATO, L.: Selective quantitative radiocardiography. Progr. Cardiovas. Dis. **5**: 1, 1962.
12. LOVE, W. D., O'MEALLIE, L. P., AND BURCH, G. E.: Clinical estimation of the volumes of

blood in the right heart, left heart, and lungs by use of I^{131} albumin. Am. Heart J. **61**: 397, 1961.

13. REJALI, A. M., MACINTYRE, W. J., AND FRIEDELL, H. L.: A radioisotope method of visualization of blood pools. Am. J. Roentgenol. **79**: 129, 1958.
14. TAPLIN, G. V., JOHNSON, D. E., DORE, E. K., AND KAPLAN, H. S.: Suspensions of radioalbumin aggregates for photoscanning the liver, spleen, lung and other organs. J. Nuclear Med. **5**: 259, 1964.
15. WAGNER, H. N., JR., SABISTON, D. C., JR., MCAFEE, J. G., TOW, D., AND STERN, H. S.: Diagnosis of massive pulmonary embolism in man by radioisotope scanning. New England J. Med. **271**: 377, 1964.
16. LOVE, W. D., AND BURCH, G. E.: A study in dogs of methods suitable for estimating the rate of myocardial uptake of Rb^{86} in man, and the effect of *l*-norepinephrine and pitressin^R on Rb^{86} uptake. J. Clin. Invest. **36**: 468, 1957.
17. LOVE, W. D., AND O'MEALLIE, L. P.: Relationship of blood flow and myocardial Rb^{86} clearance in right and left ventricles. Am. J. Physiol. **205**: 382, 1963.
18. LOVE, W. D., AND BURCH, G. E.: Estimation of the rates of uptake of Rb^{86} by the heart, liver and skeletal muscle of man with and without cardiac disease. Int. J. Appl. Radiat. & Isotopes **3**: 207, 1958.
19. BING, R. J., BENNISH, A., BLUEMCHEN, G., COHEN, A., GALLAGHER, J. P., AND ZALESKI, E. J.: The determination of coronary flow equivalent with coincidence counting technic. Circulation **29**: 833, 1964.
20. SAPIRSTEIN, L. A.: Regional blood flow by fractional distribution of indicators. Am. J. Physiol. **193**: 161, 1958.
21. DONATO, L., BARTOLOMEI, G., AND GIORDANI, R.: Evaluation of myocardial blood perfusion in man with radioactive potassium or rubidium and precordial counting. Circulation **29**: 195, 1964.
22. DREYFUSS, F., BEN-PORATH, M., AND MENCZEL, J.: Radioiodine uptake by the infarcted heart. Am. J. Cardiol. **6**: 237, 1960.
23. GUNTON, R., EVANS, J., BEANLANDS, D. S., ROTENBERG, A. D., AND PAUL, W.: Demonstration of myocardial infarction by RIFA photoscans. Abstract, Circulation **26**: 725, 1962.
24. CARR, E. A., JR., BEIERWALTES, W. H., PATNO, M. E., BARTLETT, J. D., JR., AND WEGST, A. V.: Detection of experimental myocardial infarcts by photoscanning (preliminary report). Am. Heart J. **64**: 650, 1962.
25. CARR, E. A., JR., WALKER, B. J., AND BARTLETT, J., JR.: The diagnosis of myocardial infarcts by photoscanning after administration of $Cesium^{131}$. J. Clin. Invest. **42**: 922, 1963.
26. SEVELIUS, G., AND JOHNSON, P. C.: Myocardial blood flow determined by surface counting and ratio formula. J. Lab. & Clin. Med. **54**: 669, 1959.
27. WEINBERG, S. L., CAGIRGAN, C. M., GROVE, G. R., AND SMITH, G.: Measurement of relative coronary blood flow by percordial monitoring. Am. J. Cardiol. **13**: 801, 1964.
28. MENA, I., KATTUS, A. A., GREENFIELD, M. A., AND BENNETT, L. R.: Effect of coronary blood flow on radioisotope dilution curves measured by precordial scintillation detection. Circulation Research **9**: 911, 1961.
29. TSAGARIS, T. J., KOEHLER, J. A., KUIDA, H., AND HECHT, H. H.: Studies of coronary blood flow by multiple dye dilution curves. J. Clin. Invest. **42**: 10, 1963.
30. MURPHY, P. M., FITZGERALD, E. J., O'DONNELL, L. A., JR., BURRIS, P. M., AND WILKINSON, D.: Radioactive isotope determination of myocardial blood flow by surface counting and ratio formula. Circulation **28**: 357, 1963.
31. CONN, H. L.: Use of external counting technics in studies of the circulation. Circulation Research **10**: 505, 1962.
32. COHEN, L. S., ELLIOT, W. C., AND GORLIN, R.: Measurement of myocardial blood flow using $Krypton^{85}$. Am. J. Physiol. **206**: 997, 1964.
33. KETY, S. S., AND SCHMIDT, C. F.: The nitrous oxide method for quantitative determination of cerebral blood flow in man: Theory, procedure and normal values. J. Clin. Invest. **27**: 476, 1948.
34. ROSS, R. S., UEDA, K., LICHTLEN, P. R., AND REES, J. R.: Measurement of myocardial blood flow in animals and man by selective injection of radioactive inert gas into the coronary arteries. Circulation Research **15**: 28, 1964.
35. BING, R. J., HAMMOND, M. M., HANDELSMAN, J. C., POWERS, S. R., SPENCER, F. C., ECKENHOFF, J. E., GOODALE, W. T., HAFKENSCHIEL, J. H., AND KETY, S. S.: The measurement of coronary blood flow, oxygen consumption and efficiency of the left ventricle in man. Am. Heart J. **38**: 1, 1949.
36. GELLHORN, A., MERRILL, M., AND RANKIN, R. M.: The rate of transcapillary exchange of sodium in normal and shocked dogs. Am. J. Physiol. **142**: 407, 1944.
37. WAGNER, H. N.: Regional blood flow measurements with krypton-85 and xenon-133. Dynamic clinical studies with radioisotopes. U. S. Atomic Energy Commission, Division of Technical Information, 1964, p. 189.
38. GORLIN, R., BRACHFELD, N., MACLEOD, C., AND BOPP, P.: Effect of nitroglycerin on the coronary circulation in patients with coronary artery

disease or increased left ventricular work. Circulation **19**: 705, 1959.
39. KUHL, D. E.: Section scanning for image separation. Progress in Medical Radioisotope Scanning. U. S. Atomic Energy Commission, Division of Technical Information, 1963, p. 171.
40. HINE, G. J.: Color-coded digital print-out for radioisotope scanning. J. Nuclear Med. **4**: 439, 1963.
41. BENDER, M. A., AND BLAU, M.: Data presentation in radioisotope scanning: Contrast enhancement. Progress in Medical Radioisotope Scanning. U. S. Atomic Energy Commission, Division of technical information, 1963, p. 105.
42. KAWIN, B., HUSTON, F. V., AND COPE, C. B.: Digital processing/display system for radioisotope scanning. J. Nuclear Med. **5**: 500, 1964.
43. ANGER, H. O.: Scintillation camera. Rev. Sc. Instr. **29**: 27, 1958.
44. BENDER, M. A., AND BLAU, M.: The autofluoroscope. Nucleonics **21**: 52, 1963.
45. YANO, Y., AND ANGER, H. O.: A gallium^{68} positron cow for medical use. J. Nuclear Med. **5**: 484, 1964.
46. MACINTYRE, W. J., CRESPO, G. G., AND CHRISTIE, J. H.: The use of radioiodinated (I^{131}) iodipamide for cardiovascular scanning. Am. J. Roentgenol. **89**: 315, 1963.

The Output of the Heart

The animal having expired, following exsanguination, Hales filled the left ventricle with melted beeswax and on its solidifying, measured its volume—10 cubic inches, or 160 cc. Assuming complete emptying of the ventricle in systole (we recall that Harvey, a more careful observer, did not make this assumption), and having found the pulse rate of a normal horse at rest to be 36, Hales calculated the cardiac output of the horse at rest to be 360 cubic inches or 6 liters per minute. This is a low figure, caused in part no doubt because the animal had bled to death, and the ventricular cavity was small. Further blood pressure and ventricular volume measurements in other species gave proportionate figures. For man, Hales took Harvey's estimates of two ounces as a likely volume of ventricular ejection, and calculated a cardiac output of about four liters per minute.

He noted that systole occupied only one-third of the cardiac cycle, and concluded that the run-off was therefore accomplished by the elasticity of the large vessels. He calculated the velocity imparted to the aortic column of blood in systole to be 86.7 feet per minute. He was impressed by the variability of blood pressure and heart rate under different circumstances. . . .

A broad concept of blood pressure, blood flow, blood velocity and their relations, and quantitative measurements or calculations of each—these were the great contributions made by Stephen Hales to the knowledge of the output of the heart, a contribution which has oriented all future work.—WILLIAM F. HAMILTON, M.D., and DICKINSON W. RICHARDS, M.D. *Circulation of the Blood.* Edited by Alfred P. Fishman, M.D., and Dickinson W. Richards, M.D. New York, Oxford University Press, 1964, p. 83.