Speculations to be of appreciable value should be based on (1) thorough knowledge of the past and (2) as realistic as possible prediction of the needs of the future. Then from a knowledge of these two factors, perhaps an educated guess can be made as to how the developments and capabilities from the past up to the present may be extended and synthesized with the needs of the future in order to fulfill these needs.

The past aspects of indicator-dilution technics are well covered by Fox in another section of this symposium and will not be touched on further here. The remainder of this discussion therefore will be concerned with present and future developments. All past and future developments are determined by two factors: (1) the development of completely new concepts or the variation of old concepts based on known or newly discovered information and (2) the availability or adaptation of technics and instrumentation to obtain the data required to test and utilize these concepts. Discussion will be carried out along the lines of these two considerations.

It is a truism that the development of a really new concept is indeed a very rare occurrence; obviously, therefore, no really new concepts will be covered in this presentation. The development of new technics and instrumentation, like the development of new concepts, is actually nearly always the further development, adaptation or refinement of previous technics and instrumentation. Such new developments occur with a much greater frequency than do the development of new concepts, but nevertheless are of a high order of importance. Developments of new technics in instrumentation, at present and possibly in the future, therefore will constitute a major area of discussion in this presentation; some possibly new variations of old concepts may accrue in this process.

The discussion of recent and future developments in regard to technics and instrumentation for indicator-dilution methods will be presented under two major headings: (1) development of transducers for detecting and quantitating the concentration of the indicator in the portion of the circulation under study and (2) development of new indicators for use in these technics.

First to be discussed will be detectors for recording the concentration of indicator in flowing whole blood. The difficulties of photometric measurement in whole blood are due to the fact that it requires measurement of relatively small variations in optical density in a medium of very high background optical density. Also, that these measurements must be made in the face of possible variations in this background optical density which may be produced by several nonspecific factors not related to variations in concentration of the indicator in question is discussed by Fox in another section of this symposium. These difficulties were minimized in the past in relation to oximetry for the determination of blood oxygen saturation by the use of measurements in two wavelength bands, namely the red and the infrared. Since the nonspecific variations in optical density of blood tend to occur over a relatively wide range of wavelengths, it is possible to compensate for these effects by bucking the light transmission of blood at one wavelength against that measured at another wavelength. If then one of these wavelengths is specifically affected by

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This investigation was supported in part by Research Grant H-3532 from the National Institutes of Health, United States Public Health Service.
the indicator under study, it is possible to record concentration changes of this indicator relatively independently of nonspecific variations in the optical density of blood.

The effectiveness of the oximeter when used to record the concentration of indocyanine green in compensating for such nonspecific changes as caused by injection of hypertonic solutions is illustrated in figure 1 in comparison to the high degree of susceptibility of a conventional monochromatic densitometer for indocyanine green to the same effects. That such variations in optical density of blood may occur owing to changes in a common physiologic variable such as carbon dioxide tension is illustrated in figure 2. What apparently is a satisfactory solution to the problem of devising a two-color or dichromatic densitometer for indocyanine green which retains the highly important advantage of insensitivity to variations in blood oxygen saturation has been described by Sutterer. The basis for this solution, namely the development of a compensating photocell with a balanced degree of sensitivity to light on each side of the isosbestic point for hemoglobin, is illustrated in figure 3. The effectiveness of this dichromatic densitometer in compensating for factors that produce nonspecific alterations in the background optical density of whole blood is illustrated in figure 4. It seems highly probable that the development of this instrument will result in a considerable increase in the precision of the measurements of variations in concentration of indocyanine green in whole blood.

**Figure 1**

Left panel. A series of continuous densitometric recordings at peak wavelength of 800 nm made by sampling blood from the femoral artery after injection of 1 ml. of various transparent media into the superior vena cava of a 22-kg. dog. For comparison, the dye-dilution curve obtained by injecting 2.5 mg. of indocyanine green in this same animal is also shown. Note that water and isotonic sodium chloride produced very slight upward (negative) deflections of diminished optical density of blood in contrast to the hypertonic sodium chloride solutions (5, 10 and 20 per cent), which produced increasing downward deflections of increased optical density of blood.

Right panel. Similar recordings made after the injection of 1 ml. of distilled water, 1 ml. of 20 per cent sodium chloride solution and 2.5 mg. of indocyanine green, but made with an oximeter with the circuit used for Evans blue dye. The nonspecific changes in optical density of whole blood are largely compensated for by this instrument. Indocyanine green produces an upward deflection. See text.
There are currently available a number of different types of miniature detectors whose size is such as to allow direct introduction of the transducer into the circulatory system. These include thermistors for the recording of thermal dilution curves as discussed by Hosie in another section of this symposium, and potentiometric and polarographic electrodes such as those described by Clark and Barger and discussed by Fox in another section of this symposium. The quantitative aspects of recording thermodilution curves or the concentration of dissolved hydrogen or strongly reducing substances in the blood present considerable difficulty. The development of miniature radioactivity detectors for introduction into the blood stream has not as yet been fully exploited. Miniature oximeters attached to the intracardiac end of a catheter have been described by Kramer and by Bender and Seifert. These instruments are monochromatic devices and pose considerable difficulty from the viewpoint of their susceptibility to nonspecific variations in the optical density of blood, particularly those associated with changes in the rate of blood flow at the catheter tip.

Perhaps the most promising current development along this line is the application of fiber optics to the solution of this problem by Dr. Michael Polanyi of the American Optical Company and his associates. This instrument is based on the reflection principle, and the necessity of extreme miniaturization is largely avoided by the use of fiber optics to transmit the incident and reflected light beams from the external end of the catheter to and from the blood flowing past the catheter tip. Successful operation of such an instrument either as an oximeter or as a densitometer requires use of a two-color or dichromatic assembly so that the nonspecific effects on the reflectance of blood caused by variations of blood flow past the catheter tip can be compensated for, as discussed above. By splitting the output fiber optic channel, it is possible to view the reflected light from the same blood surface within the circulatory system at two wavelength bands, one specifically affected by the indicator in question (indocyanine green) and the other specifically selected in the case of densitometry so that it is insensitive to variations in the oxygen saturation of this blood. By suitable changes in the transmission characteristics of the filters used in association with the external transducers, it is possible to use such a device either as a quantitative oximeter or as a quantitative dichromatic densitometer.

Detectors for Gaseous Indicator in Flowing Blood for Use in Dilution Technics

The quantitative aspects of dilution curves recorded by means of gaseous indicators will be greatly improved with the development of detectors capable of quantitative recording of variations in concentration of these gaseous indicators in flowing whole blood. In this regard it is worthy of mention that the oximeter as developed by Matthes and Kramer...
FIGURE 3
Comparison of spectral sensitivity of the two photocell-filter assemblies used in the dichromatic densitometer for indocyanine green and the spectral transmission of oxyhemoglobin and reduced hemoglobin. Note that the compensating photocell-filter assembly has a minimal sensitivity to wavelengths in the region of 500 μm, maximally absorbed by indocyanine green dye, and peaks in sensitivity at either side of this wavelength band. The dye-detecting photocell-filter assembly, on the other hand, has its peak sensitivity at 800 μm.

Insensitivity of the output of the compensating photocell to variations in the oxygen saturation of the blood undergoing analysis for the dye is attained by proper adjustment of the relative sensitivity of the compensating photocell on the two sides of the isosbestic point. (Used with special permission of Mr. W. F. Sutterer.)

represents the first practically usable detector for the continuous determination of a gaseous indicator, namely oxygen, in flowing whole blood. In this regard also, it is of interest that the measurement of circulation time from the lungs introduced by these workers15 as the time interval from the inhalation of oxygen or nitrogen or a foreign gas to the onset of the change in oxygen saturation of the blood passing by the ear, or some other site in the circulation, presaged the application of foreign-gas technics to the study of the circulation.

Currently a variation of the gaseous-indicator methods involving inhalation of a foreign gas in conjunction with sampling of the blood from the right side of the heart for the detection of left-to-right shunt is being explored.16 This technic involves brief inhalation of one to four breaths of nitrogen gas concurrently with continuous sampling of blood via a cuvette oximeter for oxygen saturation from various selected sites on the right side of the circulation. The brief displacement of oxygen from the alveoli caused by the inhalation of nitrogen results in unoxygenated hemoglobin traversing the pulmonary circulation into the left atrium. This reduced hemoglobin then acts as an indicator which, when shunted left to right via an intracardiac or great-vessel defect, can be detected in an abnormally short time at or downstream to the site of a left-to-right shunt into the pulmonary artery or cardiac chambers. This is exactly the same principle developed previously in conjunction with inhalation of nitrous oxide, radioactive gases or, more recently, hydrogen. This variation of the gaseous-indicator technic has the advantage that the same instrument used for detection of variations in oxygen saturation on the right side of the heart during right-heart catheterization, namely the cuvette oximeter, is also used for detection of the presence or absence of the shunted reduced hemoglobin that may occur as a result of the nitrogen inhalation. Also the reduced hemoglobin in blood from the right side of the heart can be recorded continuously and quantitatively by means of the cuvette oximeter; however, spontaneous variations in the oxygen saturation of "mixed" venous blood on the right side of the heart17 render distinction between variations due to shunted blood and those due to normally returning reduced hemoglobin in the systemic venous blood difficult. Use of this technic in conjunction with the catheter-tip oximeter being developed by Polanyi and Sutterer may provide a higher degree of sensitivity than that provided by the conventional cuvette oximeter and also will obviate the necessity of drawing a blood sample from the right side of the heart for the procedure.

Detectors for Angiocardiography
Since angiocardiography is a specific form of indicator-dilution technic in which the contrast medium serves as the indicator and the x-ray apparatus as the detector, it seems probable that the quantitative aspects of this
Variations in optical density of blood recorded from the same site in the femoral artery of a dog after three maneuvers producing "nonspecific" alterations in optical density of the blood, compared with dilution curve obtained after injections of 2.5 mg. of indocyanine green into the left atrium of an anesthetized, 14-kg. dog. These "dilution curves" were recorded simultaneously by two densitometers; one was a conventional monochromatic densitometer for indocyanine green (Waters XC100), and the other was a compensated dichromatic densitometer recently described. Although the two instruments have approximately the same sensitivity to the dye, the dichromatic device is almost completely insensitive to the nonspecific alterations in optical density caused by the changes in carbon dioxide tension produced by four breaths of 20 per cent carbon dioxide in oxygen or by injections of 1 ml. of nonisotonic solutions into the left atrium. This insensitivity of the dichromatic device also pertains to variations in blood oxygen saturation as well as to the nonspecific alterations caused by changes in blood flow through the instrument. These effects are common and are important possible sources of error in monochromatic densitometric measurements on whole blood.

The perfection of these technics bears considerable promise in regard to improving the quantitative aspects of cineangiography, both for investigative and for diagnostic purposes. Their use would, for instance, make possible concentration of indocyanine green dye in spite of its being injected in highly hypertonic solutions such as the commonly used x-ray contrast media, increases the probability of success in these attempts. An example of a simultaneously recorded cinedensogram and a dilution curve of indocyanine green in the root of the aorta of a dog is shown in figure 5. 
recording of multiple dilution curves at selected specific sites in the cardiac silhouette by means of a single cineangiocardiographic film strip obtained by only one injection of the contrast medium. Simultaneous recordings of such cinedensograms from multiple selected sites in the projected image from this angiocardiographic film would allow application of the very valuable indicator applications involving use of multiple sampling sites discussed in another section of this symposium.20 The great increase in sensitivity for variations in optical density of the cineangiogram that apparently would be achieved by this technic should also make possible a considerable decrease in the amount of contrast medium injected and hence an increase in the safety of the angiocardiographic procedure.

New Indicators

The ideal characteristics for indicators for use in conjunction with indicator-dilution technics are outlined by Fox in another section of this symposium.3 In regard to indicator dyes, the development of new dyes with much narrower absorption bands than those now currently available would be of considerable value in that it would greatly facilitate application of the very promising technics of simultaneous injection of multiple indicators and simultaneous independent recording of the dilution curves of such indicators.21 In the development of such dyes it must be kept in mind that, in addition to the usual considerations in regard to the characteristics of indicators, for use in continuous recording of circulatory dilution curves of indicator in flowing whole blood, the indicator must have the characteristic of achieving very rapid color stabilization of the dye-blood mixture immediately after contact of the dye with blood. For applications that involve injection of the indicator into a cardiac chamber such as the left ventricle and recording of the concentration of this indicator just downstream to the aortic valve, the color of the dye-blood mixture must be stabilized within a period of considerably less than 1 second. For the valuable applications of indicator-dilution technics involving multiple sudden single injections of the indicator or its continuous injection, it is of considerable value to have an indicator dye which, although it is retained within the blood stream during passage through the pulmonary circulation, is excreted as rapidly as possible during its passage through the systemic capillary circulation. This characteristic prevents accumulation of the dye during continuous or repeated injections of indicator and thus minimizes the problem of accurate quantitation of concentration changes of indicator as the background level of the dye builds up in the circulating blood stream. Recent studies22 with the indicator indocyanine green confirm that it does have the desired characteristic of very rapid stabilization of its color intensity following its addition to whole blood; furthermore, methods have been developed for allowing its quantitative determination in the presence of varying background levels of the indicator in the circulating blood.23

Recent New Concepts or Modifications of Old Ones in Relation to Indicator-Dilution Technics

Recent applications of the use of gaseous indicators, particularly in relation to diagnostic studies, have greatly facilitated and thus widened the applicability of a number of the dilution technics. The methods of using the pulmonary airway as a route for sampling of right-heart blood for the presence of dissolved gaseous indicators by the expedient of analyzing the expired air, or of introducing a gaseous indicator into the left-heart blood through the expedient of adding it to the inspired air, are of particular value. It is of interest, however, that these valuable new applications were presaged by the use by Matthes and Malikiosis15 and others of the inhalation of oxygen, nitrogen or other gases to measure the circulation time from the lung to the ear or other selected sites in the circulatory system. The technic of analyzing expired air to detect the presence of an indicator in pulmonary-artery blood is presaged...
Comparison of simultaneous dye-dilution recording and cineangiogram-density analysis made at closely adjacent sites in the aorta after injection of 0.63 mg of indocyanine green dissolved in 2 ml of 70 per cent sodium acetazolamide (urokon) into the left atrium of an anesthetized dog weighing 8.2 kg. Cine-density analysis was restricted by automatic electronic circuitry to a specific restricted time interval in each cardiac cycle in order to minimize cyclic variations in film density, not due to contrast media, which result from normal movement and change in shape and volume of the heart with each beat.

by the use of ether in the determination of arm-to-lung circulation time. Also the technique of using volatile or gaseous indicator that is largely removed during passage through the lungs to detect a right-to-left shunt is presaged by the work of Benenson and Hitzi.

The combination of the use of gaseous and nongaseous indicators recently described by Fritts and co-workers to detect arteriovenous shunts of the physiologic type, that is, blood bypassing aerated alveoli, is a most promising application of the indicator-dilution principle and is an excellent example of the use of the physical characteristics of the indicator to obtain information concerning the blood flow through specific pathways of the circulation in relation to the total blood flow through a segment of the circulation. This application is presaged by Prinzmetal's description of the combined use of a volatile indicator (ether) and a nonvolatile indicator (saccharin) in the detection and quantitation of right-to-left shunts.

It is quite obvious that application of quantitative continuous-recording methods will greatly improve the present usefulness of gaseous indicator-dilution technics.
Relationship between independent estimates of retrograde flow through the aortic valve in dogs with chronic or acute aortic regurgitation produced without thoracotomy. Retrograde flow of blood through the aortic valve was measured at necropsy at transvalvular pressure gradients covering the range recorded in vivo during the recording of the dilution curves. The retrograde flows present in vivo were estimated from these data and compared with the ratios of the areas of the immediately appearing portion of the dilution curve from the left ventricle (ALT A) to the area of the simultaneous femoral-artery curve (AFAA) recorded following injection of indocyanine green approximately 1 cm. downstream to the aortic valve. Note that the values from normal dogs do not overlap those from dogs with aortic regurgitation, and that there is a positive correlation between these independent estimates of the severity of aortic regurgitation.

During the last several years, intensive studies of this upstream-sampling technic applied under controlled conditions in dogs with acute and chronic aortic or mitral regurgitation have been underway. These studies were carried out, for the most part, in the closed-chest animal under physiologic conditions by means of technics that could be applied practically in clinical studies. It is well known that these technics have a high degree of sensitivity in the detection of valvular regurgitation and, as illustrated in figures 6, 7 and 8, under properly controlled conditions have considerable quantitative value.

Attainment and Application of High-Fidelity Dilution Curves From Cardiac Chambers and Great Vessels

Studies of the dynamic-response characteristics of conventional cardiac catheter-densitometer systems demonstrate that attainment of high-fidelity beat-to-beat recordings of the variations in concentration of an indicator in the great vessels or cardiac chambers by means of such systems is a practical impossibility unless methods for correction for the distortion associated with the traversal of the indicator-blood mixture through the catheter are devised. The practical impossibility of obtaining such recordings of indicator concentration is due to the fact that sufficiently high rates of flow cannot be obtained through such systems to allow a fast-enough dynamic response to follow the variations in indicator concentration of the frequency encountered in the central circulation (see figure 31 in reference 20, and figure 9 herein). The method of recovery of high-fidelity curves obtained by such systems as described by González-Fernández and associates utilizing the measured dynamic response of the system and the curve recorded by such a system can be used successfully for such purposes, as illustrated in figure 9. However, application of this technic is too time-consuming for most practical purposes. The use of electronic data-handling processes in conjunction with analog-computer technics, or the use of a digital computer in conjunction with an analog digital conversion system, would bring such technics into the range of practicality.

Perhaps the most promising approach to the attainment of high-fidelity beat-to-beat recordings of indicator-dilution concentration is the development of miniature detectors that can be placed directly at the site from which variations in the concentration are to be recorded. The fiber optic catheter-tip oximeter...
for recording of indocyanine green bears the greatest promise in this regard.

Except for the application of Holt in developing methods for estimating end-diastolic and end-systolic volumes of the ventricle from dilution curves recorded just downstream to the semilunar valves, possible diagnostic and investigative applications of accurate beat-to-beat recordings of indicator concentration have not been devised or exploited. These technics for determining end-systolic and end-diastolic volume, although subject to considerable question in regard to the effect of the known nonuniform-mixing situation in cardiac chambers, do, as indicated in another section of this symposium, bear some promise for the future.

It seems highly probable that beat-to-beat variations in indicator concentration in the cardiac chambers or great vessels may be altered in a characteristic fashion when these concentration changes are recorded in the
FIGURE 9
Comparison of dilution curves recorded simultaneously from the same site in the pulmonary artery of a dog by two catheter-densitometer systems (one with a slow and one with a fast dynamic response) with "true curve" at catheter tip (mathematically recovered curve). The "true curve" was calculated from the curve recorded by the slow system and the response of this system to a stepwise change in dye concentration. The slow system consisted of a 7 F. catheter 40 cm. long with an internal diameter of 1.5 cm. The blood flow through this catheter and the attached XC100A Waters densitometer was maintained at about 20 ml./min. The "fast" system consisted of an identical densitometer plus a catheter only 8 cm. long so that the dead space of the system was reduced to 0.3 ml.; consequently, its 90 per cent response time to a square-wave change in dye concentration was decreased to 0.1 second when the blood flow through the system was maintained at 250 ml./min, as compared to 4.4 seconds for the slow-system. Note the similarity in contour of the "true curve" recovered from the slow-system recording and the curve recorded by the fast system.

presence of valvular regurgitation or a left-to-right shunt. The probable ease of recording of such variations by intracardiac detectors currently under development may eventually establish them to be of considerable practical diagnostic importance. Without question, study of such high-fidelity recordings will reveal considerable information as to the mixing and streaming characteristics of the blood as it traverses the central circulation.

Multiple Simultaneous Indicator-Dilution Technics

The recently described techniques for determining continuous organ or segmental body blood flows by means of continuous injection of indicators, as presented by Fox in another section of this symposium, are of considerable potential investigative value, particularly in studies involving unsteady-state situations in the circulation.

The many other possible applications of techniques using multiple indicators with specifically selected diffusibilities and other characteristics in the study of kinetics of transfer and transport of various substances such as metabolites and drugs in the body will not be discussed here in spite of the fact that they are considered to be of a high order of importance.

Simultaneous Recordings of Dilution Curves at the Input and Output of Various Segments of the Circulation

There appears to be a strong possibility that information of value concerning the
status and characteristics of blood flow and hence possibly the status of the vasculature in given segments of or in the total circulation can be attained by determining the extent and the nature of the distortion of an indicator-blood mixture during the traversal of this mixture through these segments of the circulation or the total circulation; for example, pulmonary artery to pulmonary artery. With currently available technics that make possible injection of indicator and sampling of the resultant dye-blood mixtures from practically any site in the cardiovascular system, such technics would be applicable to the study of practically any arterial, venous or capillary segment of the circulation or combinations thereof in which the investigator may be interested. Development of technics to introduce variations of indicator concentration of various wave forms, such as a stepwise or a square-wave change in concentration, into the input of such segments of the circulation may considerably increase the sensitivity and the amount of information that can be obtained from the downstream curve and also facilitate the analytical handling of the data obtained. It is probable that such technics will have their greatest value when used in conjunction with various mathematical models in combination with analog or digital computer technics to test the hypothesis set up by these models and to devise new ones.43

Study of the Kinetics of Transport and Transfer of Various Substances

The majority of the isotopic tagging technics involving the labeling of substances that are introduced into the body and metabolized by bodily processes are in actuality indicator-dilution methods. Combination of metabolic studies of this type with conventional indicator-dilution technics involving studies of the kinetics of distribution of the metabolites in the circulatory as well as other body compartments will undoubtedly increase the scope and the value of the information obtained in such studies. As indicated above, similar technics can be used in the study of the distribution and concentration of drugs in the body and for the elucidation of the kinetics of transfer of chemical mediators from their sites of production to their target organs in the body. Information of this type is required, for instance, in studies of transient responses of the circulatory system to the onset of a stress such as exercise. Use of mathematical models and computer technics in such investigations is on the increase; this is exemplified by the study of the distribution of drugs following their intravenous injection, as described by Bellman and co-workers44 of the Rand Corporation.

In conclusion, it seems appropriate to emphasize that the basic mixing and dilution processes involved in these technics play a fundamental role in many biologic processes, and hence for the foreseeable future the importance of dilution technics and their application will continue to expand as knowledge of biologic processes increases.

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Speculations Concerning Present and Future Developments In Indicator-Dilution Technics

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doi: 10.1161/01.RES.10.3.569
_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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