UNITED STATES ATOMIC ENERGY COMMISSION

PART I. BLOOD VOLUME DETERMINATIONS
WITH RADIOACTIVE ISOTOPES AND
OBSERVATIONS ON BLOOD VOLUME
FLUCTUATIONS. PART II. INDEX OF
CARDIAC CLEARANCE

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Part I

BLOOD VOLUME DETERMINATIONS WITH RADIOACTIVE ISOTOPES

and

OBSERVATIONS ON BLOOD VOLUME FLUCTUATIONS

Part II

INDEX OF CARDIAC CLEARANCE

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Investigation Conducted at the D.C. General Hospital
Washington, D.C., Department of Anesthesiology Research
Laboratory.

Presented by:

Solomon N. Albert, B.A., M.D., D.A., F.F.A.R.C.S., F.C.C.P.
Diplomate of the American Board of Anesthesiology
Chief of Anesthesiology, D.C. General Hospital
Washington, D.C.
Clinical Instructor in Anesthesiology, George
Washington University
Hospital, Washington, D.C.
Consultant Anesthesiologist; St. Elizabeth's
Hospital, Glen Dale
Sanatorium, and National
Institutes of Health.

and

William A. Spencer, B.A., M.D.
Medical Officer, Dept. of Anesthesiology, D.C.
General Hospital,
Washington, D.C.
Instructor in Surgery, George Washington University
Hospital, Washington, D.C.

Chalom A. Albert, B.A., M.D.
Medical Officer, Dept. of Anesthesiology, D.C.
General Hospital
Washington, D.C.

Jo Shibuya, M.D.
Assistant in Anesthesiology, D.C. General Hospital
Washington, D.C.

Evelyn E. Henley, B.A., M.D.
Medical Officer, Dept. of Anesthesiology, D.C.
General Hospital,
Washington, D.C.

Contributors:

J. Richard Thistlethwaite, B.A., M.D.

Chief of George Washington Service, Dept. of
Surgery, D.C. General
Hospital, Wash., D.C.

Instructor in Surgery, George Washington University
Hospital, Washington, D.C.

Yonosuke Yamasaki, M.D.

Dept. of Anesthesiology, D.C. General Hospital
Washington, D.C.

R.D. Thergaonkar, M.D.

Dept. of Anesthesiology, D.C. General Hospital
Washington, D.C.

William O. Swan, M.S.

Talbot A. Chubb, Ph.D.

M.A. Rosen, B.S., B.A.

M. Finkelstein, Ph.D.

Elenore Zekas

Laboratory Technician

Part I.

BLOOD VOLUME DETERMINATIONS WITH RADIOACTIVE ISOTOPES

and

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Principle of Blood Volume Determinations.

Determination of blood volume with radioactive substances is essentially a dilution technique.

A measured quantity of radioactive material is introduced into the blood stream and after thorough mixing, a sample of blood is removed and analyzed for the amount of radioactivity it contains. A dilution proportion is calculated.

The calculations entail a series of computations. Count rate of accurately measured specimens containing radioactive material are reduced to a common unit for comparison. A sample of the radioactive material injected into the blood stream is prepared in a dilute form for counting purposes.

Calculations

- (1)
$$\frac{\text{Count of Dilute Standard}}{\text{Counting Time}} - \text{Ct. Bkgd./Min.} = \text{Ct. Dil. Std./Min.}$$
- (2)
$$\frac{\text{Ct. Dil. Std./Min.}}{\text{\#ml of sample}} = \text{Ct. Dil. Std./Min./ml.}$$
- (3)
$$\text{Count Dil. Std.} \times \text{Diln. Factor} \times \text{\#ml. Admin.} = \text{Total Count Admin.}$$
- (4)
$$\frac{\text{Count of Patient Spec.}}{\text{Counting Time}} - \text{Ct. Bkgd./Min.} = \text{Ct. Spec./Min.}$$
- (5)
$$\frac{\text{Ct. of Pt. Spec./Min.}}{\text{\#ml. of sample}} = \text{Ct. Spec./Min./ml.}$$
- (6)
$$\frac{\text{Total Ct. of Std. Admin.}}{\text{Ct. of Spec./Min./ml.}} = \text{Diln. Total Blood Volume}$$

To simplify the procedure all measured and known variables in the equation are made of equal magnitude.

1. Equal counting time for:
 - a. Background
 - b. Standard
 - c. Dilution Specimen
2. Equal volume of samples(constant volumes) of:
 - a. Standard
 - b. Dilute Specimen

This reduces the general equation to:

$$(7) \quad \frac{(\text{Ct. Dil. Std.} - \text{Bkgd.}) \times \text{Dil. Factor} \times \text{\#ml. admin.}}{\text{Dilution Specimen Ct.} - \text{Background}} = \frac{\text{Dil. Total B.V.}}{\text{Total B.V.}}$$

By counting the standard undiluted, we eliminate the dilution factor and obtain the following basic equation:

$$(8) \quad \frac{(\text{Ct. of Std.} - \text{Bkgd.}) \times \text{\#ml. admin.}}{\text{Dil. Spec. Ct.} - \text{Bkgd.}} = \frac{\text{Dil. Total B.V.}}{\text{in mls.}}$$

The standard count rate normally varies between 100,000 to 200,000 counts/minute. Atmospheric background count rate ranges between 175 to 250 counts/minute in a heavily shielded well-type scintillation counter. Omitting the subtraction of this very low background count from the standard count will result in an insignificant error in the final volume. For simplicity, the general basic equation is further reduced to:

$$(9) \quad \frac{\text{Count of Std.} \times \text{\#ml. admin.}}{\text{Ct. of patient sample} - \text{Bkgd.}} = \text{Diln. Total B.V.}$$

Key:

Ct. = Count
Dil. = Dilute
Diln. = Dilution
Std. = Standard
Bkgd. = Background
Admin. = Administered
Spec. = Specimen
Pt. = Patient
Min. = Minute
B.V. = Blood Volume

The Plastic Coil

In an attempt to expose to the crystal in a well-type scintillation counter accurate equal volumes for all samples, and by the same token eliminate all possible technical errors in measurement with pipettes, the "Plastic Coil" was devised. The coil is made of polyethylene tubing which is inserted and fixed in the well counter. All samples are drawn into or injected through the coil tubing for radioactivity analysis. The results obtained by measuring radioactivity in liquid samples with the plastic coil, were compared with the standard method of aliquot counting both in vitro and in vivo experiments.

Preparation of the Plastic Coil

Polyethylene tubing with an internal diameter of 1.77mm (Clay-Adams, PE-260) is wound around a 5mm glass tube at a distance of two inches from the distal end. A two-layered coil is made, both ends of the polyethylene tubing running in the same direction. (Fig. 1 & 2) The coil fits a standard well-type scintillation counter. The two ends of the coil are firmly secured with adhesive tape to the lead shielding of the well counter. One end of the coil tubing is connected to a syringe, to which a three-way stopcock is adapted. (Fig. 3) The syringe acts as a pump and the other end of the tubing is left free for injecting or aspirating samples or to flush the coil with normal saline in order to decontaminate it. In the experiments performed, all samples were counted in duplicate. Background count was checked immediately prior to counting a sample, spot checked between samples, and upon completion of an experiment. All counts were made with the preset constant time. All samples were of equal volume.

The total fluid volume was calculated as follows:

$$\frac{(10) \text{ (Counts of Std. - Bkgd.)} \times \text{\#ml. admin.}}{\text{Counts of sample - atmospheric Bkgd.}} = \text{Total volume}$$

The standard was counted both as an undilute and diluted standard. Results obtained by counting the diluted standard 1:100 were compared with those obtained by counting undilute standard.

Repeated volume measurements were made of the initial volume by administering additional doses of red cells tagged with CR-51. Total fluid volumes were calculated in the following manner.

- a) by total doses of standard injected.(Formula 1)
- b) by taking a control count and calculating the result as per single dose of standard.

(Formula 11)

$$(11) \frac{(\text{Counts of Std.} - \text{Bkgd.}) \times \# \text{cc admin.}}{\text{Counts of sample} - \text{Control spec. bkgd.}} = \text{Total B.V.}$$

(Control background is the count of activity taken on sample of fluid prior addition of a new dose of tagged cells.)

The results of in vitro experiments are summarized in Chart I.

There was no statistically significant difference between volume measurements made with the coil or aliquot techniques:

- a) measured and estimated volumes ($p=0.8$ to 0.5)
- b) serially estimated volumes using both Formula 1 and Formula 2, ($p=9.8$ to 9.3)
- c) estimated volumes obtained by Formula 1, when compared with those obtained by Formula 2, ($p=0.7$ to 0.6)
- d) volumes estimated with dilute and undiluted standard, ($p=0.9$ to 0.7)

The mean difference in estimated volumes between the two techniques employed ranges between -3.31 to 2.59% .

Changes in volume were effected by removing 100ml of active solution from the total gross volume and replacing it with non active saline solution. The difference between the estimated and measured volumes fell in the range of -2.5 to 7.8% with a mean difference of $9.5 \pm 1.9\%$.

Chart I

ESTIMATED VOLUMES WITH CR-51 TAGGED ERYTHROCYTES AVERAGE RESULTS OF FIVE IN VITRO EXPERIMENTS

Volume No.	Measured Volume (ml.)**	(1)*** Estimated Mean Volume (ml.)	(1)*** Range of Difference (Per cent)	(2)**** Estimated Mean Volume (ml.)	(2)**** Range of Difference (Per cent)
A. Coil Method--Standard Undiluted					
1	3,530	3,501 ± 40	-4.8to+1.1	- - - - -	- - - - -
2	3,550	3,546 ± 38	-3.2to+2.2	3,595 ± 86	-4.6 to +8.5
3	3,570	3,549 ± 27	-2.7to+1.1	3,560 ± 16	-1.7 to +0.5
4*	3,590	- - - - -	- - - - -	3,576 ± 56	-3.3 to +5.4
B. Coil Method--Standard Diluted 1:100					
1	3,530	3,510 ± 39	-4.3to+2.3	- - - - -	- - - - -
2	3,550	3,553 ± 36	-2.7to+2.1	3,604 ± 85	-3.5 to +9.2
3	3,570	3,558 ± 25	-2.4to+1.2	3,569 ± 12	-1.1 to +0.5
4*	3,590	- - - - -	- - - - -	3,585 ± 60	-3.5 to +6.0
C. Test-Tube Method--Standard Undiluted					
1	3,530	3,385 ± 19	-5.5to-2.4	- - - - -	- - - - -
2	3,550	3,448 ± 24	-5.2to-1.1	3,517 ± 66	-6.0 to +4.4
3	3,570	3,446 ± 36	-6.1to-0.3	3,454 ± 74	-8.3 to +2.7
4*	3,590	- - - - -	- - - - -	3,580 ± 55	-4.3 to +3.5
D. Test-Tube Method--Standard Diluted 1:100					
1	3,530	3,478 ± 25	-2.8to+0.2	- - - - -	- - - - -
2	3,550	3,506 ± 29	-3.0to+1.8	3,615 ± 81	-3.9 to +7.4
3	3,570	3,543 ± 42	-4.0to+2.6	3,530 ± 60	-4.8 to +3.1
4*	3,590	- - - - -	- - - - -	3,678 ± 57	-2.1 to +6.5

* Five hundred milliliters of active saline were removed from the gross volume and replaced with 500ml. of non-active saline.

** Thirty milliliters of tagged cells was added for the volume estimation after removal of 10ml. aliquots for test-tube counting. Therefore, increments of only 20ml. in total measured volumes.

*** Formula 10 employed for volume estimations.

**** Formula 11 employed for volume estimations.

A 4% error was obtained in a series of experiments using the plastic coil and counting undiluted standard. This included repeated determinations with and without gross changes in the total volume.

Blood volume determinations made on a series of patients using the two techniques were compared--plastic coil versus aliquot--also, diluted versus undiluted standard counting. The difference between results obtained by the two methods were negligible, (less than 3%). Repeated total blood volume determinations were made using successive doses of tagged cells in order to reduplicate the initial blood volume measurement and to determine blood loss after blood donation. The results varied within a range of 5%.

The use of the plastic coil placed in a well-type scintillation counter enables determination of fluid volumes with greater speed and with a high degree of accuracy and reproducibility. The results were comparable and in many instances, more accurate than those obtained by the test-tube and aliquot method. All technical errors are reduced. Pipettes, calibrated equipment, and large quantities of glassware are eliminated from the routine procedure. Breakage, spillage, and time wasted in washing and decontaminating glassware are reduced to a minimum.

Red cells tagged with CR-51 do not adhere to polyethylene tubing. Radioactive Iodinated human serum albumin (RISA) in saline adheres to the tubing, while dilute solution of RISA in plasma or whole blood present no problems of coil contamination in concentrations of 0.2 microcuries/milliliter.

Variations in the temperatures between 10° and 40° C show a 1% variation in count due to an increase of volume, and a negligible variation was noted in the range of 20° to 40° C.

Chart II (Summary)

Volume Determinations--Comparison Between Diluted and Undiluted Standard

Measured Vol. in cc	Undiluted Standard		Diluted Standard	
	<u>Coil</u>	<u>Aliquot</u>	<u>Coil</u>	<u>Aliquot</u>
3,530	3,501	3,385	3,510	3,437
3,550	3,546	3,448	3,553	3,506
3,570	3,549	3,446	3,558	3,543

Calculated from Total Activity

Preparation of Tagged Cells with CR-51

The procedure for preparing red cells tagged with CR-51 takes two to three hours. In order to reduce this lengthy procedure, a stock preparation of tagged cells is made.

One millicuries of Sodium Chromate (CR-51) is added to a pint of O Rh negative blood, preserved in ACD solution. The bottle of blood is gently shaken every 15 minutes for a period of one hour, at room temperature. The blood is then filtered through a recipient blood set into a series of sterile centrifuge tubes, each to contain about 40ml. of blood. The centrifuge tubes are capped and stored in a refrigerator at 4-6° C. Round bottom 50ml. centrifuge flasks are most convenient.

To prepare a dose of tagged cells, the supernatant fluid, (plasma), from one of the centrifuge tubes is removed, under sterile conditions. The centrifuge tube is then filled with chilled normal saline solution and shaken thoroughly. The mixed centrifuge bottle is centrifuged for twenty minutes at 2000rpm. The supernatant fluid is removed, and the tagged washed red cells are resuspended in normal saline to approximately 50mls. Two 20ml. standard doses are removed to be administered to the patient, leaving a 10ml. sample for counting.

A larger number of doses can be prepared at one time. Washed cells of several centrifuge tubes are mixed in a single large sterile container, and a representative 10ml sample is removed for counting as standard, which would be valid over a period of twelve hours.

Tagged red cells washed and resuspended in saline can be used within a 24 hour period. In the procedure described, the tagged red cells are washed only once. Repeated washing and handling of the red cells enhance their breakdown. The amount of free CR-51 trapped between the cells after one single washing is insignificant. (Fig. 4)

A trial with two millicuries of sodium chromate (CR-51) added to a pint of blood was made in order to reduce the amount of cells administered for each determination of blood volume. The volume of packed cells necessary to prepare a dose of standard was, consequently, reduced 50%. The calculated volumes obtained varied over a wider range and results could not be accurately duplicated. Counts taken on consecutive blood samples varied between 3-10%.

The possible explanation for this discrepancy is mainly a physical difficulty to obtain a proper and even distribution of a small number of highly radioactive cells in a large volume. The loss of a few cells during manipulation will result in larger errors.

By using large volumes and low activity, we have dispensed using calibrated equipment, or weighing syringes, and limited our glassware to commercial 10 and 20ml syringes only.

Calibration of the Plastic Coil

For radiological exposure safety purposes, it is important to determine the amount of radioactivity the patient receives with each dose of standard administered.

The amount of radioactive material, as calculated from the quantity employed to activate red cells, is inaccurate due to the fact that there is a loss during the washing procedure.

In order to calibrate the plastic coil and accurately measure the quantity of isotope administered, a test solution containing five microcuries of sodium chromate in 10ml. of blood or plasma is accurately prepared. The activity of the radioisotope is calculated from the date of assay. This test preparation, therefore, contains 0.5 microcuries/ml. The plastic coil in the well counter is filled with this preparation and a 10 minute count taken. Atmospheric background count, taken over 10 minutes, is subtracted from the final count obtained.

A graph is prepared by plotting the minute count versus microcuries/ml. The graph is only applicable for the particular coil with which the count of the assay solution was made. The number of microcuries in all sample counts made in this calibrated coil can be calculated from the graph. (Fig. 5)

To calculate the number of microcuries, the following formula is used:

Total amount of
microcuries admin. = Microcuries/ml. x #ml. administered.

Use of RISA with the Plastic Coil

RISA in normal saline has a tendency to adhere to polyethylene tubing. RISA in plasma or blood in 0.2 microcuries/ml. is easily washed out and does not adhere to the coil tubing. The routine procedure of counting the standard in the plastic coil had to be modified.

One hundred microcuries of RISA is added to 500ml. of N. saline solution. This preparation, therefore, contains 3-4 microcuries/20mls. undiluted standard, which can be used over a period of 6 days. For each blood volume determination, the patient receives 10-20mls. of this undilute standard preparation. For counting purposes, a dilute standard is prepared. One to two ml. of the undilute standard. Once the dilute preparation is calibrated with the undilute saline preparation, this diluted preparation will be used for counting purposes in the coil for determining the total activity administered to the patient.

A dilution factor is established between the dilute plasma (or blood) preparation, and the undiluted standard saline preparation. The dilute standard preparation in plasma (or blood) is first introduced into the coil and a count taken. This is followed by counting the undiluted standard prepared in normal saline. The exact proportion of dilution is calculated and a dilution factor is established. The dilute standard plasma (or blood) preparation is labeled with the dilution factor and the contaminated plastic coil discarded and replaced by another coil.

$$(12) \text{Diln.} = \frac{\text{Undiluted Std. in count - Bkgd.}}{\text{Factor Dilute Std. in plasma (or blood) - Bkgd.}}$$

Since the decay of I-131 in the dilute and undilute standard preparations run parallel, one can determine the total amount of counts administered to a patient by counting the dilute standard, subtracting atmospheric background, and the result multiplied by the dilution factor and by the number of mls. of undilute standard administered to the patient.

The dilution factor is only used for the particular undilute standard saline preparation.

For each new preparation of 500ml of RISA standard in saline, a new dilute standard should be prepared, a new dilution factor determined and the contaminated coil replaced.

It is important to emphasize that when standardizing the dilute plasma (or blood) preparation with the undilute standard, one should count the dilute standard first, since the latter does not adhere and contaminate the polyethylene tubing.

The procedure for blood volume determination with RISA is as follows: 1) Administer into an accessible vein 10-20ml of the undilute saline standard, 2) Count the dilute standard in the plastic coil, 3) Calculate the total number of counts the patient received, and 4) Remove a heparinized blood sample from the patient and count. The following is the formula used:

$$(13) \text{Blood Volume} = \frac{(\text{Ct. Dilt. Std. - Bkgd.}) \times \text{Dilt. Factor} \times \text{\#cc undilt. Std. admin.}^*}{\text{Specimen count - Bkgd.}}$$

(10)

* All specimen samples of equal volume. All counts on preset time--equal time.

Determination of Blood Volume with Tagged Cells

A sample of CR-51 tagged red cell suspension administered to the patient is injected or aspirated into the plastic coil and a count taken. The amount of radioactivity it administers is obtained from the graph, (Fig. 5), prepared for the particular coil in use.

The amount of CR-51 injected per dose does not exceed 20 microcuries per 150 lbs. body weight. In children, we use one microcuries per 10 lbs. With repeated blood volume determinations, the maximum amount of CR-51 circulating at one time should not exceed 150 microcuries in adults. In the event that the patient is losing blood, the number of doses the patient receives is dependent upon the amount of blood lost. In practice, we do not administer more than 12-18 microcuries of CR-51 to an adult per dose for a single blood volume determination. The dose is increased for subsequent blood volume measurements.

The measured volume of tagged cells is administered intravenously through an 18 gauge needle. Injecting cells under pressure with a fine bore needle may cause damage to the red cells and enhance hemolysis giving inaccurate results due to the elimination of free CR-51.

Fifteen minutes is allowed for proper distribution of the tagged cells. A sample of blood is removed in a heparinized syringe from any accessible vein. The mixed sample is gently injected to fill the coil tubing completely.

To calculate blood volume, Formula 14 is used.

$$(14) \text{ Blood Volume} = \frac{\text{Count of Std.} \times \text{\#ml. administered**}}{\text{Patient Spec. count} - \text{Bkgd. count}}$$

** Preset constant counting time for standard, blood samples and background

Patients having previously received radioactive material should have a background count made on a blood sample prior to administration of a dose of tagged cells.

Formula 15 is used in calculating the blood volume:

$$(15) \text{ Blood Volume} = \frac{\text{Count of Std.} \times \text{\#ml. administered}}{\text{Specimen count} - \text{Patient Background}}$$

Micro-hematocrit determinations are made in duplicate on all blood samples.

To calculate the various components of the circulating blood volume, we use the following formulae:

$$\begin{aligned} \text{Total red cell volume} &= \text{Total B.V.} \times \text{Hct.} \\ \text{Plasma volume} &= \text{Total B.V.} - \text{red cell volume} \\ &\text{or} \\ \text{Plasma volume} &= \text{Total B.V.} \times 1 - \text{Hct.} \end{aligned}$$

A study was made to determine whether there is a difference in the distribution of tagged red cells in blood samples taken from various sites.

Fifteen minutes after administration of tagged cells, blood samples were withdrawn from eight different blood vessels simultaneously; left femoral vein, right femoral vein, left femoral artery, left antecubital vein with tourniquet, right antecubital vein, left antecubital vein, and right external jugular vein. The variations in counts between all the samples was minimal and made no significant change in the calculated blood volume.

A catheter introduced into the median cephalic or femoral vein can be used for injecting tagged red cells and removal of blood at desired intervals.

With hypotension, shock, or obstruction to circulation, there is pooling of blood and mixing time is longer. Thirty minutes should be allowed for adequate mixing and even distribution. Accurate timing of proper mixing can be obtained by precordial counting.

By removing blood samples at various time intervals from two different sites, one can establish the amount of blood trapped in a specific area. The technique was used to evaluate the amount of blood trapped in the pelvic area and lower extremities in cases of obstruction to the venous return to the heart.

The blood samples were taken from an arm vein and the femoral vein for comparison. (Fig. 7)

Determination of Blood Volume with RISA

The procedure for determining blood volume with RISA is similar to that of red cells tagged with CR-51. The only variation being that the diluted standard is used for counting purposes in the plastic coil. Formula #13.

To determine plasma volume, the following formula is used:

$$\text{Plasma Volume} = \frac{\text{Total count administered}}{\text{Plasma count} - \text{Background}}$$

$$\text{Total Blood Volume} = \frac{\text{Plasma Volume}}{1 - \text{Hematocrit}}$$

$$\text{Red Cell Volume} = \text{Blood volume} - \text{Plasma Volume}$$

RISA adheres to polyethylene tubing to some extent to the inner wall of the vein in which it is administered. One cannot inject RISA through an indwelling polyethylene catheter, nor can one withdraw blood specimens from the site of injection.

Red cell volume cannot be accurately determined from the total blood volume as measured with RISA and the hematocrit reading. The hematocrit as determined on a mixed venous sample is not representative of the total space into which RISA actually diffuses.

In normal individuals, blood volumes determined with RISA approximate results obtained with T-1824 (Evans-Blue Dye Technique). Both techniques measure a 10-15% higher value than the tagged cells technique.

The Combined Use of Tagged Cells and RISA.

Twenty ml. of RISA standard in saline, containing approximately 2-4 microcuries of I-131, and 20ml. suspension of washed O Rh negative red cells tagged with CR-51 containing approximately 18 microcuries were injected, either as individual doses or in combination, into an accessible peripheral vein. Ten (10) ml. blood samples were withdrawn from the femoral vein in heparinized syringes.

A portion of the whole blood specimen was counted. Hematocrit determinations were made in duplicate by the micro-hematocrit technique.

The following calculations were made:

$$\text{Plasma} \frac{(\text{Counts I-131 Dil. Std.} - \text{Bkgd.}) \times \text{ml. admin.} \times \text{Dil. Factor}}{\text{Volume I-131 count in Plasma} - \text{Background}}$$

I-131 count in whole blood specimen would equal
(1.0 - Hematocrit) x plasma I-131 count.

$$\text{Blood Volume (I-131)} = \frac{\text{I-131 Standard total count}}{(1.0 - \text{Hct.}) \times \text{plasma I-131 count}}$$

$$\text{Blood Volume (CR-51)} = \frac{\text{Counts of CR-51 std.} \times \text{ml. admin.}}{\text{Total count of Spec.} - \text{Bkgd.} - (\text{I-131 in whole blood determined by Formula 7})}$$

Blood volume as measured with RISA fails to show the stability in measurements when compared with the CR-51 tagged cell technique. As a rule, blood volumes determined with RISA tend to become progressively larger with each successive measurement. This steady increase is due to a resulting 'leak-out' of isotope from the vascular bed. (Fig. 8)

The difference in measurements between a RISA and CR-51 tagged cell technique of blood volume widens in patients with protein imbalance, vasoconstriction, shock and cirrhosis of the liver.

The widest differences in blood volumes were observed in patients affected with chronic debilitating diseases. (Charts 3 and 4)

Chart 3

Serial Blood Volume Determinations with RBC tagged with CR-51 and RISA I-131

Case #102 Liver Cirrhosis B.S.P. 12%
48 yrs. C.M. Wt. 119 lbs. Ht. 5'6"

<u>RISA I-131</u>				<u>O Rh. Neg. RBC CR-51</u>		
B.V. cc	P.V. cc	RC.V cc	Ht.%	B.V. cc	P.V. cc	RC.V. cc
7100	4450	2650	37	3850	2400	1450
9150	5850	3000	36	3925	2500	1425
7100	4800	2300	32.5	4650	3150	1500
7400	5075	2375	32	4650	3175	1475
8600	5750	2850	33	4600	3100	1500
9400	6350	3050	32.5	4700	3175	1525

Chart 4

Single Dose Blood Volume Studies with CR-51 RBC and RISA I-131

Case #105 Pancreatitis
48 yrs. W.M. Wt. 176 lbs. Ht. 6'

<u>RISA I-131</u>				<u>O Rh. Neg. RBC CR-51</u>		
B.V. cc	P.V. cc	RC.V. cc	Ht.%	B.V. cc	P.V. cc	RC.V. cc
6900	4500	2400	36	3875	2475	1400
7275	4650	2625	36	3900	2500	1400
8775	5625	3150	36	3825	2450	1375
10550	6825	3725	33.5	4100	2725	1375

Serial Blood Volume Determinations with Single Dose
of O Rh Negative Cells Tagged with 15-20 Microcuries
of CR-51.

Red cells, when carefully handled and injected into a normal patient, survive several days. Tagged cells in a mixed blood sample measures the intravascular volume. The central venous hematocrit reflects the proportion of red cells of this measured volume. Therefore, changes occurring in total blood volume may be attributed to fluctuations in plasma volume.

Studies conducted on normal patients have shown that there is approximately a 5% loss of the total standard count administered in a 24 hour period. This loss is attributed to the hemolysis of cells, elution elimination, and decay.

$$(16) \text{ Blood Volume} = \frac{\text{Initial Std. count} - (5\% \text{ decay for each day})}{\text{Specimen count} - \text{Atmospheric Bkgd.}}$$

Formula 16 is used to measure fluctuations in blood volume by following variations in count of blood samples with a single dose injection of tagged cells.

The Use of the Plastic Coil in a Shunt System.

The plastic coil is made of polyethylene tubing which can be sterilized by emersion in 1:1000 aqueous Zepharin solution for 24 hours. The coil is rinsed with normal saline solution and placed in a well-type scintillation counter. One end of the coil is attached to an arterial catheter or needle with a three-way stopcock and the other end to a venous catheter or needle. The three-way stopcock is used to administer tagged cells to flush the coil, and to instill a slow infusion of heparin, in order to maintain an open circuit.

The coil can be used for intermittent blood sampling and injection of isotope. A femoral catheter is inserted and a syringe is attached to the coil for injecting tagged cells, or withdrawing blood samples through the coil for counting.

The latter technique has proven to be of value for serial blood volume determinations in the operating room. (Fig. 9)

Results of Studies on Blood Volume.

1. Normal Fluctuations in Blood Volume

Total blood volume may increase as much as 500ml. following ingestion of food and fluid. The blood volume returns to the original level within a period of 3-4 hours. Measurements taken during sleep show a rise, which may be the result of a relative hypotension and decreased renal filtration. All changes are actually reflected in plasma volume changes. (Fig.10)

2. Administration of N. Saline and 5% Dextrose in Water Infusion

Patients receiving intravenous infusions of either isotonic saline solution or 5% dextrose in distilled water, show a transient increase in blood volume, which lasts approximately 2-3 hours. Normal saline solutions seldom caused an increase of blood volume equal to the amount actually infused. Dextrose, 5% in water, on the other hand, causes a transient increase far greater than the amount administered. The difference in response between these two solutions may be attributed to the osmotic effect of the Dextrose molecule. (Fig. 11)

Administration of DEXTRAN Preparations in Saline and in Glucose.

Blood volume changes were determined in a group of forty patients using O Rh negative red cells tagged with CR-51. One group of twenty patients received 200ml of Dextran in normal saline, and a second group of twenty patients received 200ml of Dextran in 5% Dextrose in water. The amount administered was accurately measured by syringes. Blood samples were withdrawn after 20 minutes and 2 hours.

There was a rise in blood volume with Dextran in 5% Dextrose averaging 400-500ml--almost 100% over the amount actually administered. In some rare instances there was 200-300% increase. The increase in blood volume observed with Dextran in saline was proportional to the amount infused.

Dextran is of a high molecular weight and remains 12-24 hours in the circulation. One may foresee the dangers of administering Dextran indiscriminately in large quantities in patient suffering from blood loss. A needed blood transfusion superimposed on previous Dextran infusion may result in a failing circulation due to an overload. Dextran in 5% Dextrose in water, may temporarily pull into the circulation a large quantity of fluid and result in an unpredicted temporary hypervolemia.

Vasodilation and Vasoconstriction

Blood volume determinations were made before and after induced blood pressure changes.

a) Hypotension by vasodilation

Morphine SO₄

Pentothal (R) Na

Arfonad (R)

In all instances, there was an increase in the CR-51 blood volume determination with an associated fall in the hematocrit reading.

b) Hypertension by vasoconstriction

Neosynephrine (R)

Pain or apprehension. The blood volume decreased with a proportional rise in the hematocrit reading.

Blood volume measured with RISA demonstrated minimal fluctuations with induced hypotension or hypertension.

Using both isotopes simultaneously, RISA and CR-51 tagged R.C., blood volume measured with RISA tended to be 10-40% higher than the results obtained with CR-51. With induced hypotension by vasodilation CR-51 blood volume measurements demonstrated an increase and the values tended to approximate the volume initially determined with RISA. (Fig. 12)

This phenomenon of compensatory vasoconstriction, to limit the area through which a diminished blood volume circulates, is important for the maintenance of an adequate minute volume flow of blood to vital organs.

Patients that developed severe hypotension with premedication and during induction of anesthesia, demonstrated a wide difference in blood volume as measured by the combined isotope technique. These patients, in essence, were hypovolemic, but compensated by vasoconstriction.

The Effect of Removing 25% of the Blood Volume.

Serial blood volume determinations with CR-51 tagged red cells were made following rapid removal, by venesection, of 25% of the estimated total circulating blood volume.

In some instances, this amount of blood loss did not result in changes of the final hematocrit reading or radioactivity count of blood samples taken from the patient over a period of several hours. A repeat estimation of blood volume by the administration of a second dose of tagged cells demonstrated a decrease in volume equivalent to the amount of blood removed. Over a period of 48 hours, there is established a gradual hemodilution which is reflected in a decreasing radioactivity count and falling hematocrit. (Fig. 13)

In some instances, a different pattern was encountered. During the process of bleeding the patient, and continuously counting the rate of activity as the blood is withdrawn through the plastic coil placed in a scintillation well counter, the radioactivity counts fell steadily, indicating prompt hemodilution. Administration of a second dose of tagged cells resulted in measurement of a new blood volume that did not commensurate with the amount of blood removed. The total red cell volume measured a loss equivalent to the red cell volume removed during the bleeding process.

When hypotension occurred, hemodilution was rapid, and the patients became restless. Vasodilators favored rapid hemodilution resulting in an increased blood volume with a concomitant drop in the hematocrit reading. This effect could be reversed when vasopressors were administered.

Serial Measurements of Blood Volume Fluctuations.

The circulating blood volume is a dynamic quantity. It is interesting to be able to follow the rate and extent of variations in blood volume under various physiological conditions.

Procedure:

Blood volume is determined by the routine method, red cells tagged with CR-51. (Pages 12-14)

A scintillation probe, with a 2 inch crystal is placed over the precordium or placed in a position to point toward a collection of blood which has little tendency to vary in volume. A minute count is taken at the time the blood sample for measuring the blood volume is removed.

The count obtained with the scintillation probe is compared to the count of the blood sample as measured in the well counter. A proportion is established between the precordial count and the blood sample count.

$$\begin{array}{lcl} \text{Precordial} & \text{Precordial probe ct./min. - Bkgd.} & \\ \text{Count} & = & \hline \text{Factor} & \text{Blood sample ct./min. - Atmos. Bkgd. with probe} & \end{array}$$

Since changes in blood volume are reflected as variations in the radioactivity count, one can follow, therefore, blood volume fluctuations by continuously measuring changes in the radioactive count over the precordium directly.

To convert the counts obtained with the scintillation probe over the precordium into volume determinations, the following formula is used:

$$\begin{array}{lcl} \text{Blood} & \text{Count Std./Min. x \#ml administered} & \\ & = & \hline \text{Volume} & \text{Precordial count - Atmos. Bkgd. with probe/} & \\ & \hline & \text{Precordial Factor} & \end{array}$$

Blood volume fluctuations measured by this method were checked by counting blood samples withdrawn at the time the precordial count reached a stable counting rate level. Marked changes in stroke volume and heart volume, as seen during blood loss and after replacement of fluid, will alter the factor. A new factor should be determined.

Placing the scintillation probe over the precordium and taking repeated counts enables one to determine the time at which the count rate becomes steady. This technique permits the reduction of the waiting time for proper mixing to take place. It is specially valuable in shock and sluggish circulation.

The Dilution Meter Computer.

A computer was devised which will automatically compute dilution, the result appearing as a direct meter reading. The computer was initially designed to perform one single operation--determination of blood volume with red cells tagged with CR-51 using the plastic coil.

$$\text{Blood Volume in mls.} = \frac{\text{Count of Std.} \times \text{\#ml administered}}{\text{Dilution count} - \text{Bkgd. (Patient or atmospheric)}}$$

The equation is converted into an electrical analogue:

$$I = \frac{V}{R_2 - R_1}$$

Whereby: I = Current
V = Voltage
R = Resistance

The amperage is read directly on an appropriately calibrated m.a. meter.

The impulses from a scintillation counter are scaled by appropriate factors and fed to rotary stepping switches. Resistances are attached to each point on the stepping switches.

Three sets of rotary stepping switches are used for each part in the above equation. There are 25 positions on each switch, allowing a total of 15,625 counts. The stepping switches will accurately register at a rate of 20-25 impulses per second.

A precision 5 inch microampere meter is used to indicate the final reading.

Automatic control circuitry has been incorporated to render the device as simple and as error free as possible.

At the completion of the background count, the position of the stepping switches of the background is transferred to the dilution stepping switches in a negative position, thus accomplishing the required subtraction.

Weak concentration of radioactivity are scaled by a factor of 10, and highly radioactive material, (hot standard), is scaled by a factor of 1000.

Special Features.

The computer has a 'lock-in' system, whereby, background counts and standard counts are retained and cannot be inadvertently erased by turning on the reset switch. This allows running a series of blood volume determinations when using the same standard and atmospheric background count. The dilution count is reset after each reading and the computer is ready for the next specimen count. The background count or the standard count can be zeroed at will, and new information introduced into the computer.

When counting a dilute proportional standard, a manual standard is incorporated in the nature of a variable resistance.

Safety Mechanical Features.

There are three push button contact switches representing the three values found in the equation--background, standard, and dilution--each having an appropriate neon light to indicate registered counts.

The meter will only read when all the components of the equation have been taken into account. In the event of an error, whereby, the background count is higher than the dilution count, a dilution specimen count being too high, a red light indicates an error in the procedure.

The timer is a 5 minute, 'Eagle' timer, with automatic reset.

Calculation of Red Cell Volume.

The meter is shunted across with a variable resistance calibrated in percent hematocrit. A hematocrit determination is made, and the result is not on the calibrated dial; the meter then reads the calculated red cell volume.

Correction for Volume of Standard Administered.

A control marked 5, 10, or 20ml. of standard automatically multiplies the standard count in the computer to correct for the volume of standard injected.

The overall error due to inaccuracies inherent in the meter, and scaling factors used to activate the stepping switches is 3%. It is felt that this error compensates for the possible human error of manipulation, and computation. It permits inexperienced personnel to determine blood volume.

The computer is also adaptable for direct percentage distribution. (Fig. 14)

The Value of Blood Volume Determination.

The following summaries of four representative cases demonstrate the value of blood volume studies made prior to surgery and during the immediate post operative period.

Case #1. 48 yr. C.M. with P.B. of 120/90; p. 90; Hct. 41%. chronically ill, had a cystostomy performed under general anesthesia in a 15° Trendelenberg position. There was no blood loss during the procedure. As the patient was recovering and regaining consciousness, the operating table was straightened. Suddenly, the blood pressure started to drop steadily and pulse rate increased. Two minutes later a diagnosis of cardiac arrest was made. The head of the table was lowered and positive oxygen applied. Cardiac massage was instituted and within three minutes, the heart resumed its normal spontaneous activity.

Circulating blood volume was measured to be 200ml with a 39% hematocrit. The patient was hypovolemic. Administration of 500ml of blood restored partially the blood volume. The patient had an uneventful recovery.

Case #2. 58 yr. M. underwent a partial gastric resection. Twenty-four hours post operatively, the hematocrit dropped from 40% to 31%, pulse rate increased to 160/min. and B.P. dropped to 90/60mmHg. It was suggested that the patient was suffering from internal hemorrhage and should be given a blood transfusion.

he circulating blood volume was measured, and found to be 7800ml. The patient was hypervolemic and was suffering from an overloaded circulation. Restriction of fluids over a period of 12 hours resulted in a steady drop in pulse rate and a rise in blood pressure. Hematocrit improved and the patient had an uneventful recovery.

Case #3. 49 yr. patient with auricular fibrillation and cancer of the esophagus, had a preoperative blood volume of 3800ml. with a 42% hematocrit. Esophagectomy was performed. At the termination of the procedure, the patient was cyanotic. Pulse 160, B.P. 70/?. It was suggested that the patient was hypovolemic and suffering from blood deficit. Repeated blood volume determinations resulted in 3900ml circulating blood, and a 39% hematocrit. Instead of transfusions, the patient required digitalization because of myocardial failure.

Case #4. 58 yr. F. underwent partial gastric resection. In the immediate post operative period the patient went into shock. Hematocrit 38%, B.P. 70/40, Pulse 150. It was suggested that the patient was suffering from post anesthetic shock. Blood volume determination resulted in 2800ml circulating blood volume. After 1000ml. transfusion a repeat blood volume determination was made which registered an increase of only 300ml. Intra-abdominal bleeding was diagnosed and 2500ml. of clotted blood was removed from the peritoneal cavity.

Part II. INDEX OF CARDIAC CLEARANCE

Cardiac output expressed in milliliters per minute changes under a variety of normal and abnormal physiological conditions. There is a constant process of adaptation in order to maintain an adequate minute blood flow to vital organs.

The techniques presently used to determine cardiac output are based on differential gas analysis or on the principle of measuring the average dilution of a substance introduced into the circulation, as it leaves the heart.

Radioactive isotopes injected into the peripheral circulation are used to measure the average dilution volume that leaves the heart by analyzing the radioactivity of arterial samples taken in succession, or by taking an activity rate tracing with a counter over an arterial blood flow. (1) (2)

Huff, et al, (3 and 4) simplified the standard procedure by simply placing a scintillation counter over the left parasternal region between the 1st and 2nd rib, over the arch of the aorta and recording the rate of dilution.

Procedure:

A scintillation probe with a two inch crystal is centered over the 2nd left anterior intercostal space. Red cells tagged with CR-51 containing approximately 20md. suspended in 10ml. of saline are injected in the right antecubital vein. (Fig.15) The rate of activity as the isotope leaves the heart is measured and recorded on an Esterline-Angus recorder attached to a counting rate meter. The curve obtained is extrapolated to zero activity in order to obtain a single cycle passage of the radioactive material through the heart. (Fig. 16)

The cardiac output is measured by establishing the number of counts passing by the heart as compared to the total standard counts administered. The result being in multiples of blood volume dilution.

Formula used: (1)

$$\begin{array}{lcl} \text{Cardiac} & & \text{Blood volume x Cf. x 1 minute} \\ & = & \hline \text{Output} & & \text{Count under the curve} \end{array}$$

The same result is obtained by comparing the area under the extrapolated curve as measured with a planimeter, with the minute area at stabilization--the time at which a blood specimen is withdrawn for blood volume determination. The result is then multiplied by the measured blood volume.

Formula used: (2)

$$\begin{array}{lcl} \text{Cardiac} & & \text{Area B (over 1 minute) x blood volume} \\ & = & \hline \text{Output} & & \text{Area A (over 1 minute)} \end{array}$$

Difficulties encountered

1. In order to obtain curves that can be properly interpreted, large amounts of radioactive isotope should be administered. The number of determinations that can be performed is limited.
2. In about 10% of cases, the curves obtained on the recorder cannot be properly interpreted.
3. Difficulty in delineating and extrapolating the dilution curve accurately. In our experience, no two members of the staff extrapolated the curves in the same manner, and no two results were equal.

Cardiac output is of relative value. In order to observe changes, we are mainly concerned in relative changes rather than in absolute values. It was felt that if the procedure could be simplified to permit repeated determinations and at the same time to be able to duplicate results, cardiac output determinations would be of valuable aid in studying cause and effect as related to the heart.

The measurement of the average dilution with which a dose of isotope administered leaves the heart is an indication of the cardiac output. Simultaneous rate recording of radioactivity were taken and compared with results obtained by taking an accumulated count over a 60 second period, starting from the time a rise in count rate is detected proportional to a 60 second count taken at the time of stabilization--the time the blood specimen was withdrawn for blood volume determination.

$$\text{I.C.C.} = \frac{60 \text{ sec. ct. at stabilization} - 60 \text{ sec. Bkgd.}}{60 \text{ sec. initial ct.} - 60 \text{ sec. Bkgd.}} \times 100$$

The proportion in counts taken over these two periods, was labeled "Index of Cardiac Clearance".

The variations in the Index results were compared with the cardiac output measurements made using the dilution curve recording by studying the effect of Adrenalin, vasodilators, and cardiac depressants on the cardiac output. The Index results were parallel to the cardiac output results. (Fig. 17)

The normal Index was established to vary between 55 and 60.

During the course of the initial study, it was felt that the Index reflected a composite picture of cardiac output and blood volume.

Comparison Between
Cardiac Output & Index of Cardiac Clearance
F.G. 60 yrs. C F Pernicious Anemia

	Huff Methd.	Index	Ht.	B.V.	P.
Before Therapy	6200ml/min.	87.75	15%	1850	110
5 day Ther. & Bld. Tran.	4875ml/min.	82.00	22%	2300	100
10 day Ther.	4625ml/min.	74.60	325%	2450	80

The results obtained with the Index of Cardiac Clearance were consistant and could be duplicated within 1-2%.

A mathematical interpretation of the Index substantiated the clinical impression that the Index is a composite picture of cardiac output and blood volume.

The following formula was derived to convert the Index determination into approximate cardiac output ml/minute. (Figs. 18 and 19)

$$\text{Cardiac Output} = \text{B.V.} \times \frac{1}{\frac{100}{\text{Index}} - K}$$

$$K = 0.70$$

In Vitro Experiments

A piston pump system and a fluid reservoir were used to simulate the heart action. The stroke volume and rate of the pump were varied as well as the volume of fluid in the reservoir.

The minute output of the pump was measured volumetrically over a 30 second period and compared with the output calculated from the Index, and the output calculated from the dilution curve. Results are shown in Table #1.

The overall average difference with the measured output was +6.3% as calculated from the Index, and +6.3% as calculated from the dilution curve.

Table #1

In vitro experiments with measured
output from a regulated pump

A. Comparison of results as calculated from the INDEX

Total # of experiments	18	Average	+ 6.3%
# of experiments with results greater than the measured output	14	with an average	+10.8%
# of experiments with results less than the measured output	4	with an average	- 5.6%

B. Comparison of results as calculated from the
dilution curve

Total # of experiments	17*	Average	+ 6.3%
# of experiments with results greater than the measured output	12	with an average	+13.8%
# of experiments with results less than the measured output	5	with an average	- 5.2%

* One curve could not be interpreted

Comparison of Results Obtained in a Series of Studies
in Patients

The results of cardiac output as determined by the Direct Fick Method are compared with the dilution curve technique, the Index, and the calculated cardiac output from the Index value.

Table #2

Cases Compared with Direct Fick Method

Case #	Fick	Index	Calc. C.O.	Dilt. Curve	Blood Volume
382	7.6L	76.0	7.25	6.67	4460
404	7-9L	78.0	7.92	7.10	4600
337 *	Sed. 3.85L Exer. 6.74L	76.	5.26	4.27	3242
424 *	Pul. 10.7L Sys. 5.1L R-L 5.9L L-R 0.3L	74.0	6.53	7.64	4257
417 *	Anal. 7.7L Rest 5.4L O ₂ 7.2L Exer. 15.8L	70.0	9.62	10.38	7000

* Fick determination was performed several months earlier

Table #3

Comparison of Results Obtained in a Series of Studies
in Patients--Cases Compared with Huff Method-
Dilution Curve

Case #	B.V.	Index	Calc. C.O.	Huff Method
122	4950	75.0	7821	9820
324	4168	71.0	5885	6456
325	4275	64.0	4960	5589
329	3260	83.0	6455	7009
335	3175	65.0	3785	4300
336	5300	53.0	4460	5600
339	4950	79.3	8745	9778
341	3575	83.0	7080	9158
344	3742	70.5	5285	5297
345	2941	76.4	4775	5090
353	2848	64.0	3305	2760
357	3800	64.3	4405	3878
358	3210	82.1	6185	6033
365	2844	81.5	5480	5108
368	4588	68.0	5960	5975
381	4310	66.1	5288	5030

Table #4

Results with Huff Method of Determinations

(Repeat Cases)

Case #	Blood Volume	Index	Calo. C.O.	Huff Method	Remarks
319	4960	69.5	6730	7994	Before Anes.
"	5166	62.6	5680	6708	After Anes.
351	5670	64.0	6575	9186	Pre-Surgery
"	3760	53.2	3169	2420	Post-Surgery
412	5270	73.0	7860	11,412	Pre-Surgery
"	4930	75.0	7790	7193	Post-Surgery
416	5300	70.0	7280	11,050	Pre-Surgery
"	5080	79.0	8976	12,390	Post-Surgery

The results of our studies substantiated the fact that the Index of Cardiac Clearance has a certain significance and value. It may well develop to be a practical and simple method for evaluating cardiac functions, and effect of drugs on the normal and diseased myocardium.

A conversion table has been worked on whereby the index is converted into a factor which is multiplied by the blood volume, giving an approximate cardiac output value.

A nomogram has also been prepared for calculating cardiac output. (Fig. 20)

Conversion Table for Indices

Cardiac Output = Blood Volume x Factor

<u>Index</u>	<u>Factor</u>	<u>Index</u>	<u>Factor</u>	<u>Index</u>	<u>Factor</u>
40	0.555	60	1.035	80	1.818
41	0.575	61	1.065	81	1.869
42	0.595	62	1.096	82	1.927
43	0.617	63	1.127	83	1.980
44	0.637	64	1.160	84	2.041
45	0.657	65	1.193	85	2.099
46	0.679	66	1.227	86	2.159
47	0.701	67	1.263	87	2.227
48	0.723	68	1.299	88	2.294
49	0.746	69	1.335	89	2.358
50	0.769	70	1.374	90	2.433
51	0.793	71	1.412	91	2.506
52	0.818	72	1.451	92	2.584
53	0.843	73	1.493	93	2.667
54	0.869	74	1.536	94	2.747
55	0.894	75	1.580	95	2.833
56	0.922	76	1.623	96	2.941
57	0.949	77	1.669	97	3.020
58	0.977	78	1.718	98	3.125
59	1.006	79	1.767	99	3.225

$$\text{Cardiac Output} = \frac{\text{Blood Volume}}{\frac{1}{\text{Index}}} - 70$$

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Figure 1

Figure 2

Figure 3

% Free Cr51

Figure 4

Counts / Mt.

Figure 5

Figure 6

Figure 7

*DISTRIBUTION OF R.B.C. TAGGED WITH Cr^{51} ,
and
RADIOACTIVE IODINATED HUMAN SERUM ALBUMIN I^{131}*

Figure 8

Figure 9

Figure 10

Figure 11

Figure 12

Figure 13

Figure 14

Figure 15

Figure 16

Figure 17

$$C.O. = \frac{Cs}{\frac{Cc}{V}}$$

$$B.V. = \frac{Cs}{\frac{CRf}{V}}$$

$$Cs = B.V. \times \frac{CRf}{V} = \frac{B.V. \times CRf}{V}$$

$$\frac{Cm}{V} = \frac{Cc}{V} + \frac{CRi (1-E)}{V}$$

$$\frac{Cc}{V} = \frac{Cm}{V} - \frac{CRi (1-E)}{V} = \frac{Cm - CRi (1-E)}{V}$$

$$CRf \quad CRi \quad \therefore \quad CRi = k \times CRf$$

$$\frac{Cc}{V} = \frac{Cm - CRf (1-E) k}{V}$$

$$C.O. = \frac{\frac{B.V \times CRf}{V}}{\frac{Cm - CRf (1-E) k}{V}} = \frac{B.V. \times CRf}{Cm - CRf (1-E) k}$$

$$C.O. = B.V. \times \frac{CRf}{Cm - CRf (1-E) k} = B.V. \times \frac{1}{\frac{Cm}{CRf} - (1-E) k}$$

$$\text{Index of Cardiac Clearance} = \frac{CRf}{Cm} \times 100$$

$$C.O. = B.V. \times \frac{1}{\frac{100}{\text{Index}} - K}$$

C.O. = Cardiac Output per minute in mls.
 Cs = Total count of standard per minute injected
 Cc = Total count rate under the curve per V.
 V. = Volume of blood exposed to the crystal
 B.V. = Total blood volume
 Crf = Final count rate at stabilization per V.
 Cm = 1st minute total count per V.
 CRi = Count rate at end of 1st minute per V.

Figure 18

$$K = (1-E) k = 0.70$$

CARDIAC OUTPUT

Figure 19

INDEX

C.O. ml./min.

S.V. ml.

Figure 20