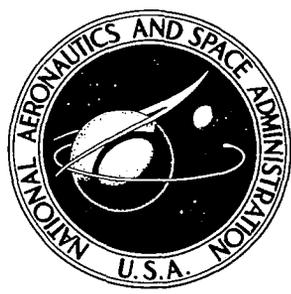


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## REVIEW OF PHYSIOLOGICAL MEASUREMENT TECHNIQUES FOR APPLICABILITY TO SPACE FLIGHT CONDITIONS

*by T. M. Fraser*

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*for*

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APPLICABILITY TO SPACE FLIGHT CONDITIONS

By T. M. Fraser, M.S., M.D.

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for

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## SOME PHYSIOLOGICAL MEASUREMENT TECHNIQUES FOR SPACE LABORATORIES

To develop a program of biomedical testing for use in manned space laboratories it is necessary to review the nature of the expected problems as they are seen today. Information from the Mercury, Vostok, Voshkod, and Gemini missions, and from U. S. and foreign laboratories, has provided a comprehensive picture of much of the requirement for manned earth-orbiting vehicles, and no doubt still further information will become available from the Apollo and future missions. By the time a large manned space laboratory can be launched, or assembled in space, more will be known about the response of man to the problems that beset him in short or medium duration earth-orbiting or lunar missions, and much will have been done to protect him from potential or actual hazard. Some is already known, and more will be known, about man's response to the accelerations of launch, re-entry, and impact, to short duration buffeting, to heat, cold and humidity, to variation in atmospheric pressure, and exposure to hyperbaric oxygen or to mixed gas atmospheres for 30 days or so. More will also be known about man's response to weightlessness, restriction and confinement. Procedures, techniques, and devices may also have been developed, if required, to protect him from any potential hazard associated with weightlessness, and from the effects of radiation. Extrapolations of such knowledge, however, even on the basis of all that is acquired in the intervening period, will provide only a speculative indication of how he will respond and how well he will perform in a very prolonged mission. Thus an organized re-examination of his response under space laboratory conditions is needed to determine the occurrence of any psychological or physiological decrement with time.

It must be assumed that the vehicle under consideration will have the requisite space, habitability, and facilities, along with an adequate environmental control system with comprehensive, reliable, environmental monitoring which will provide immediate and accurate information on the spacecraft environment to both ground control and the spacecraft occupants. Such being the case, the necessity for continuous routine physiological monitoring of the crew will become minimal, since the results would merely reflect extreme changes in the environment, better observed directly on environmental monitors. Continuous physiological monitoring is essentially second order environmental monitoring. Thus, physiological monitoring systems can be reserved for use in data collection during experimental procedures, or at regular and routine intervals. From the resulting information the extent of any time-dependent decrements can be evaluated.

In a manned space laboratory, problems of launch and re-entry will be only a routine feature, and, in fact, the vehicle might well be assembled in space. Consequently the major areas of concern will be those associated with continued orbital missions, and probably will be much the same as they are now, namely, the effects of weightlessness, radiation, confinement and work cycling, atmospheric contamination and inter-current illness, accidental injury and decompression. Primary consideration will probably be given to the psychophysiological response to weightlessness and radiation. Since each of these has an actual or potential widespread effect on body function, much incidental information will be obtained on the total body response to the total environment, which can be amplified by suitable experimentation. Thus, it need not be construed that the collection of biomedical data should be rigidly confined to certain areas, nor that it should adhere to a rigid protocol. Particularly in a long duration mission, with a high calibre of scientific observer among the crew, and a high index of curiosity, the objective and direction of research may well change, and as knowledge is gained, it will be possible to extend investigation to greater depth and wider fields.

With respect to weightlessness, studies to date have indicated the potential occurrence of detrimental effects primarily related to the cardiovascular, hematologic, locomotor and metabolic functions, with perhaps some effect on the respiratory, equilibratory, and renal systems. Further studies will determine the significance of these reactions and will separate the effects of immobility from weightlessness or reduced gravitation. Studies on radiation have shown that the major effects are observed on the alimentary, integumentary, hematological and neurological systems, with further effects on cellular repair and immunological response. In addition, the adrenocortical and adrenomedullary functions are ultimately bound up with the body response to stress, as are certain aspects of neurological function, while fluid and electrolyte balance, and perhaps changing enzyme patterns, provide an indication of the integrity of the internal body environment.

It is desirable then to devise techniques and instrumentation to measure the body response over the entire gamut of body function. To organize this approach it is advisable to examine man's capacities in terms of various related body function systems. This paper examines techniques in the fields of cardiovascular and respiratory function, and discusses approaches to anthropometry and body composition, with orientation towards identifying those techniques which might be most useful for inclusion in the specifications for work to be performed in a manned space laboratory. It is emphasized that in many cases much development is yet required, not only in validation of some of the more esoteric techniques discussed, but in determining protocols and procedures appropriate to a confined and weightless situation, and in integrating the requirements of equipment, skill, and available time with other demands.

The study is not intended to be a comprehensive physiological review, particularly in the area of cardiovascular physiology; for example the entire field of cardiac electrical activity has been ignored, largely because it has been so widely examined elsewhere. Similarly no consideration has been given to measurement of heart rate and cardiac morphology. Emphasis instead has been placed on examining areas where the information to be gained is significant, but where techniques available do not readily lend themselves to use in space, or where a multitude of available techniques requires consideration.

It might also be mentioned that the physiological measures discussed here represent three areas from a group of ten, originally selected as encompassing a major portion of human physiological function. The other areas comprise metabolism, alimentary physiology, thermal exchange, neurophysiology, endocrine physiology, hematology, and the areas of immunology and histology. Continued studies might well include the other areas along with a discussion of techniques of sample collection and processing, development of specialized instrumentation, the integration of measurement systems covering several functional areas, and the requirement for data handling, display, and information retrieval. It is not feasible, however, to include all of these at this time.

Certain guidelines have been accepted in discussing the various approaches to measurement. It is assumed that a habitable environment will be provided. Serious constraints, however, will exist with respect to available volume, weight, and power, while the absence of gravitational force will grossly interfere with the capacity to perform gravity dependent tasks. Thus many common laboratory procedures will not be feasible. In addition a trained physician may or may not be present, and even if present could hardly be expected to be master of all the complex skills that could be demanded of him. In addition, for ease of maintenance and optimum reliability, simplicity of instrumentation must be emphasized. Furthermore, where the experimental subjects are operational astronauts, as they will be, the techniques employed must be those which involve minimal violation of the subject, minimum consumption of his time, and no toxic contamination of the atmosphere, actual or potential. Thus, while reference may be made in this study to techniques of considerable complexity involving severe violation of the subject, emphasis is placed on those providing optimization of subject participation, reliability of data, simplicity of execution and instrumentation, and no hazard either immediate or future.

The study is divided into three distinct sections, namely cardiovascular, respiratory, and anthropometric (body composition). Each section is further divided into particular topics of interest. Recommendations are made at the end of each topic. References to the literature cited are found at the end of the study.

SECTION 1  
CARDIOVASCULAR FUNCTION  
CARDIAC OUTPUT

From a teleological point of view it may be considered that the function of the cardiovascular system is to provide a continued, adequate supply of oxygenated blood to the brain, to the body organs responsible for maintenance and support, and to the musculature. From a more pragmatic point of view, if the veins, the right heart, and the lung vasculature are considered as a low pressure reservoir, and the systemic arteries as a high pressure reservoir, the function of the heart is to pump blood from the low to the high pressure reservoir. As one of the most significant measures of the integrity of this function, and of the extent of its adaptation to internal and external stimuli, the timed volume output of blood from the heart is paramount. By definition the cardiac output is the timed product of the stroke volume and the heart rate. Since heart rate is readily measured, the complexities of measurement lie in obtaining values for the stroke volume.

Since it is not practicable to measure stroke volume directly in man, and barely practicable even in animals, numerous ingenious techniques have been developed for indirect measurement. Many of these, however, are very complex and require considerable violation of the subject, such as intracardiac catheterization, arterial infusion, and arterial puncture, and cannot be considered readily acceptable. Some of these are discussed below, however, along with others considered more appropriate.

### Methods involving the peripheral pulse

On contraction, the left ventricle ejects a volume of blood into the aorta from whence it is passed along the arterial tree. In addition to passage along the aorta, the ejected blood also produces a pressure pulse within the vessels, the amplitude of which is measurable as the difference between the systolic and diastolic pressure, or the pulse pressure. This pressure pulse distends the vessel and of course is most apparent in the aorta. There is obviously a relationship between the pulse pressure and the stroke volume, but this relationship is complicated by the varying distensibility and resistance of the arteries involved. Numerous attempts have been made to derive equations linking stroke volume and pulse pressure. Most of these have been on an empirical basis, whereby the pulse pressure reading is modified by some constant derived from the blood pressure without any deliberate allowance being made for the arterial distensibility. Examples of the type of formulae used are shown on Table (1) from the work of Warner and his associates (303).

In another approach, Bolie and his colleagues ( 37 ) prepared a nomogram (Figure 1) for the determination of stroke volume from blood pressure on the basis of an equation developed by Starr (312) which allows for modification of blood pressure by age.

These methods of course are highly empirical but provide in some cases quick and useful approximations of the stroke volume, with the minimum of measurement, particularly if carefully pre-calibrated by an indirect Fick or dye method.

Bazett and his associates ( 27 ), advocated the use of the pulse wave velocity as an index to the percentage increase in volume of an artery over a given range and thereby hoped to account for the factor of arterial distensibility. Hamilton and his associates at the University of Georgia ( 152, 269, 146 ), extended the technique and found it useful for measurement of cardiac output in dogs, but observed that while there is a relationship between pulse wave velocity and arterial distensibility, the relationship is relative and not absolute, and is modified by the capacity

TABLE 1

COMPARISON OF VALUES FOR STROKE VOLUME OBTAINED BY EIGHT VARIATIONS OF THE AORTIC PRESSURE PULSE METHOD AND BY THE FICK AND DYE METHODS IN MAN

No. of comparisons:.....	TEST CONDITION					
	Exercise		Tilt 70°		Press. applied to body and tilt in sitting position	
	10		7		12	
Stroke volume by Fick or dye method <sup>1</sup>	Mean 128 cc.	S. D. ±15 cc.	Mean 65 cc.	S.D. ±13 cc.	Mean 82 cc.	S.D. ±14 cc.
% Difference from Fick or dye value						
<i>(A) Methods Using a Pressure Difference and a Proportionality Constant Only</i>						
1) Pulse pressure method, $SV = (P_s - P_d)k_1$	5	±9	38 <sup>2</sup>	±21	3	±13
2) Dicrotic pressure method, $SV = (P_s - P_d)k_2$	-28 <sup>2</sup>	±15	37	±41	-2	±20
3) Systolic area method, $SV = (P_{Sa})k_3$	-13 <sup>2</sup>	±12	1	±12	0	±14
4) Mean distending pressure method, $SV = (P_{md})k_4$	-12 <sup>2</sup>	±11	25 <sup>2</sup>	±15	3	±13
<i>(B) Above Methods with Correction for Changes in Ratio of Systolic to Diastolic Drainage<sup>2</sup></i>						
5) Pulse pressure method, $SV = k_5(P_s - P_d) \left(1 + \frac{T_s}{T_d}\right)$	27 <sup>2</sup>	±10	39 <sup>2</sup>	±23	3	±16
6) Dicrotic pressure method, $SV = k_6(P_s - P_d) \left(1 + \frac{T_s}{T_d}\right)$	-15 <sup>2</sup>	±12	36 <sup>2</sup>	±29	-1	±21
7) Systolic area method, $SV = k_7(P_{Sa}) \left(1 + \frac{T_s}{T_d}\right)$	6	±14	0	±17	0	±16

Definition of symbols: SV, stroke volume; P<sub>s</sub>, systolic pressure, P<sub>d</sub>, diastolic pressure; P<sub>Z</sub>, pressure at dicrotic notch; P<sub>Sa</sub>, product of mean rise above diastolic pressure during systole times the duration of systole; k<sub>1</sub> through k<sub>4</sub>, proportionality constants obtained by dividing the resting value for stroke volume (Fick or dye) by the respective resting pressure difference; k<sub>5</sub> through k<sub>7</sub>, proportionality constants obtained by dividing the resting value for stroke volume by the product of the resting pressure difference times the value  $\left(1 + \frac{T_s}{T_d}\right)$ ; (T<sub>s</sub> and T<sub>d</sub>) duration of systole and diastole.

1. Resting control values for stroke volume averaged 108cc. with S. D. of ±30cc. 2. Statistically significant systematic difference; P value less than 0.02. 3. Changes in heart rate produce changes in the relative duration of systole and diastole and thus in the relationship of systolic to diastolic drainage. This would be expected to alter the relationship between stroke volume and the pressure differences used in these methods since the pressure pulse results from the net volume increase, that is volume ejected minus the volume running off. In methods 5, 6 and 7 a time factor T<sub>s</sub>/T<sub>d</sub> only is used. Source: Warner et al. (330)

### Stroke Volume Nomogram

Starr's Equation  $SV = 100 - 0.6 A + 0.3 SP - 1.1 DP$   
 DP = Diastolic Pressure (mm. Hg), SP = Systolic Pressure (mm. Hg)  
 A = Age (years), SV = Stroke Volume (ml.)

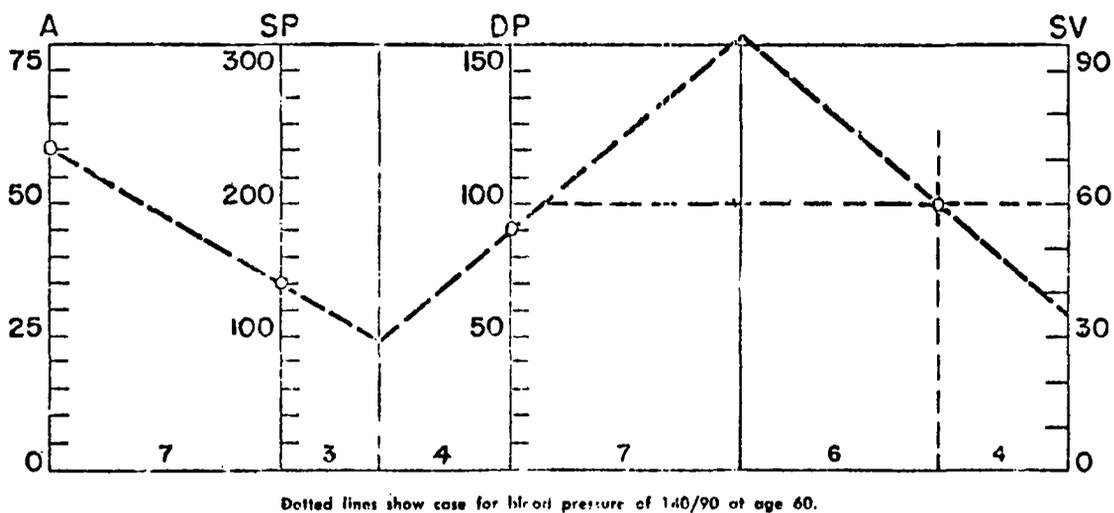


Figure 1

Source: Bolie et al. ( 37 )

TABLE 2

Factors for the Prediction of Stroke Volume.  
per m<sup>2</sup> Body Surface, from the Pulse Pressure.

Pressure	Volume Factor	Pressure	Volume Factor	Pressure	Volume Factor
mm Hg	ml	mm Hg	ml	mm Hg	ml
20	0	100	81	180	140
30	10	110	90	200	148
40	21	120	100	220	155
50	31	130	108	240	161
60	42	140	115	260	167
70	52	150	122	280	173
80	62	160	128	300	179
90	71	170	134		

Source: Remington et al. ( 269 )

of each segment of an artery at the beginning of the pulse. Consequently pulse wave velocity cannot provide information on absolute distensibility. In man, in particular, because of wide variability in aortic size at diastolic pressure in a given individual, and because of still further changes associated with age, physiological conditions, body size, and disease, the technique is not reliable.

Consequently, this group ( 269 ) went on to develop a method independent of distensibility measures. By experimental stretching of rings cut from human aortas and measurement of pressure volume relationships, Remington showed that regardless of previous history, age, or aortic size, the average increase in aortic volume per unit pressure rise is very similar. The actual volume at any diastolic pressure will vary widely, but the change in volume with pressure is more constant. Furthermore, at pressures between 20 and 100 mm Hg there is virtually a proportional relationship between pressure and volume which tends to fall off above the upper level.

From values of stroke index derived from 83 determinations of cardiac output by the Fick principle, along with simultaneous arterial brachial pressure pulse, Remington then adjusted the values of the previously noted pressure volume curves to conform to those which would be expected on the basis of stroke index calculated by the Fick procedure. The stroke index represents stroke volume per square meter and is used to diminish differences occurring by reason of body size. The final figures are shown in Table (2) which permits prediction of the stroke volume from the difference between the volume factors associated with systolic and diastolic pressures.

In examining this method it is apparent that there is considerable room for error in prediction. The pressure-volume data used to derive the table are averaged over different age groups and physical conditions, with, in each case, fairly large standard deviations applicable to the data points. On top of this, these averaged data are then manipulated somewhat arbitrarily to accommodate to averaged Fick cardiac output data, which in turn may have an inherent error of  $\pm 10\%$  ( 283 ). It is not surprising that Remington found a discrepancy of 18.6% between cardiac outputs obtained from his

table and those obtained by the Fick principle. At the same time, with known individuals it would be possible, by doing Fick type cardiac output estimation at rest and under varying conditions of exercise, to develop in controlled laboratory conditions a constant ( or constants ) which would be applied to the table for use in an orbiting laboratory.

Warner and his associates ( 330 ) in Wood's laboratory, utilized this principle of pre-calibration by a Fick method to determine a constant which would link stroke volume to the systolic/diastolic pressure ratio. Using an equation, the derivation of which is clearly expressed in their paper, they showed that:

$$SV = kP_{md} ( 1 + S_a/D_a ) \quad ( 1 )$$

where

SV = stroke volume

k = constant

P<sub>md</sub> = end systolic mean distending pressure  
(measured)

S<sub>a</sub> = area under curve of systolic arterial  
pressure corrected for mean time of  
pulse transmission.

D<sub>a</sub> = area under curve of diastolic arterial  
pressure corrected for mean time of  
pulse transmission.

Details of the logic and method should be consulted in the original paper. Using this technique they obtained a close correlation, with a 9% standard deviation, between their method and estimations made by direct Fick and dye methods. Since the technique calls for catheterization into the subclavian artery, however, it cannot be given much consideration for use in space vehicles.

Still more sophisticated methods have been developed by Hamilton and his group ( 152, 145, 268, 146 ) using the time relationships of arterial pulse contours. Hamilton points out, however, that although pulse contour methods have applicability to dogs with a high degree of correlation with direct Fick methods, they are not suitable for use in man for the reasons previously noted. Essentially the technique requires the initial development of tables showing the net volume uptake per square meter of body

surface in different portions of the arterial tree under different pressures, along with the transmission times of the pressure pulse to these different portions under the same pressures, and the diastolic drainage times.

On the basis that the stroke index is the sum of the arterial uptake and arteriolar outflow, or drainage, per square meter of body surface the stroke index can be shown to be given by the following equation:

$$SI = U + U \frac{(T_s - T_w)}{T_c - T_s + T_w} \quad ( 2 )$$

where

SI = stroke index

U = arterial uptake per square meter  
( from tables )

T<sub>s</sub> = time of systole

T<sub>w</sub> = weighted average drainage time

T<sub>c</sub> = total time of cardiac cycle

In addition to having doubtful applicability to man, however, this method also requires intra-arterial catheterization and hence cannot receive much consideration for use in orbiting laboratories.

#### Methods involving cardiometry

Cardiometry is the term given to the direct measurement of changes in cardiac volume occurring with the events of the cardiac cycle. Most cardiometric methods require open thoracic surgery and are not applicable to man.

The use of x-ray techniques, however, has permitted another approach to cardiometry. Hamilton <sup>( 146 )</sup> has reviewed some of the methods used. Straight thoracic x-ray with timed short exposures made during systole and diastole provides a picture of cardiac shadow through the cycle, from which volume calculations can be made. Since x-ray sees only in one plane, however, the three-dimensional action of the heart is ignored, and cardiac outputs so calculated are persistently underestimated. More sophisticated techniques using cardiac x-ray kymography suffer from the same disadvantages.

Empirical constants obtained from Fick or dye methods can be applied to correct the resulting values ( 165 ).

Another method involves the quantification of light intensity resulting from x-rays passing through the body and impacting on a fluorescent screen. Measurement is made by means of a photomultiplier system which, with suitable processing, provides a record somewhat similar to that of a mechanically recorded ventricular plethysmogram. Again, however, calibration factors must be applied to the record from cardiac output measures calculated by other techniques ( 273 ).

Further approaches have been made by the use of infusions of radio-opaque material into the left ventricle with subsequent study of the intraventricular shadow by cineangiocardiology ( 58, 141, 285 ) but the technique is complex and calls for catheterization of an artery.

There is no doubt that valuable information can be obtained through the use of x-rays. In the orbiting space laboratory, however, the information obtainable by straight x-ray, or even kymography, can be found more accurately, and in some cases more simply, by other methods, while that obtained by sophisticated x-ray methods would not appear to justify the violation of the subject and the complexity of the instrumentation and techniques. The additional radiation exposures, even using the most advanced techniques, would be considered generally undesirable.

#### Methods involving the Fick Principle

The Fick principle, which was enunciated by Fick in 1870, states that the rate of uptake of a reference material by an organ is equal to the difference in concentration of that material in the intake and output blood stream. In other words,

$$\frac{dM}{dt} = F_o C_o - F_i C_i \quad ( 3 )$$

where

M	=	quantity of reference material
F <sub>o</sub>	=	rate of flow out of organ

$C_o$  = concentration of material in outflow  
 $F_i$  = rate of flow into organ  
 $C_i$  = concentration of material in inflow

The integrated form of the equation is shown as:

$$M = \int_{t_0}^{t_{\infty}} (F_o C_o - F_i C_i) dt \quad (4)$$

If the flow rate and the concentration are independent of the time interval T and if  $F_o = F_i$  at all times, the equation may be represented as:

$$M = F(C_o - C_i) T \quad (5)$$

or, in its more usual form:

$$F = \frac{M}{(C_o - C_i) T} \quad (6)$$

In determining cardiac output in relation to oxygen consumption the equation becomes:

$$\dot{Q} = \frac{\dot{V}_{O_2}}{C_{a_{O_2}} - C_{\bar{v}O_2}} \quad (7)$$

where

$\dot{Q}$  = blood flow per unit time  
 $\dot{V}_{O_2}$  = oxygen consumption per unit time  
 $C_{a_{O_2}}$  = arterial  $O_2$  content  
 $C_{\bar{v}O_2}$  = mixed venous  $O_2$  content

In a very thorough analysis of the potential errors that arise in the application of this equation, Stow (319) emphasizes the requirement for constant flow and concentration, and observes that even in "steady state" conditions changes occur in both the lung volume and pulmonary blood

volume. He observes further that in practice when a needle or catheter is used for withdrawal of blood samples at a constant rate, the resulting samples yield a time average concentration and not the volume average concentration that the equation demands. He goes on to illustrate other potential errors arising from irregular mixing in the blood stream, inconstancy of flow volume, and velocity. Fishman and his associates (100) have also commented on the unreliability of the Fick equation in the unsteady state engendered by entering or leaving a hypoxic condition, a point which may have some application to the determination of cardiac output in a space laboratory.

Because of the various actual and potential errors, cardiac output as estimated by the direct Fick principle is considered reliable at best only to within  $\pm 10\%$ . The direct Fick procedure, using oxygen as a reference material, would nevertheless appear to be the most reliable method available. Its application calls for a measure of  $O_2$  consumption, a measure of arterial  $O_2$  content, and of mixed venous  $O_2$  content. While the  $O_2$  consumption is a relatively simple measure, that for arterial  $O_2$  content requires a sample of arterial blood; while in order to obtain a representative sample of mixed venous blood intra-cardiac catheterization is necessary. These complexities render the procedure impracticable for use in an orbiting space laboratory. (See Respiratory Section).

An obvious respiratory application of the Fick principle lies in utilizing  $CO_2$  as the reference material instead of  $O_2$ . In this situation the equation becomes:

$$\dot{Q} = \frac{\dot{V}_{CO_2}}{C_{\bar{v}CO_2} - C_{aCO_2}} \quad (8)$$

- where
- $\dot{V}_{CO_2}$  = carbon dioxide production
  - $C_{\bar{v}CO_2}$  = mixed venous carbon dioxide content
  - $C_{aCO_2}$  = arterial carbon dioxide content

Carbon dioxide production is readily measurable. Arterial  $\text{CO}_2$  content can be very closely approximated by measuring the  $P_{\text{CO}_2}$  in a sample of end-tidal air and subsequently deriving the  $\text{CO}_2$  content from a prepared  $\text{CO}_2$  dissociation curve. The major problem lies in obtaining a value for the mixed venous carbon dioxide content.

One approach towards obtaining this value is to rebreathe oxygen in a closed system until the  $\text{CO}_2$  concentration in the system reaches a plateau representing equilibrium with the mixed venous concentration. Because of problems arising from the recirculation of the  $\text{CO}_2$  produced, and slowing of the evolution of  $\text{CO}_2$  from the venous lung blood as a rebreathed air tension approaches that of blood <sup>(146)</sup>, it is difficult to establish where this end point occurs. A technique for determining this end point was proposed by Defares and his colleagues <sup>(77)</sup>, and has been still further developed by Garza <sup>(124)</sup> and Luft. This method is currently in regular use and continued development in Luft's laboratory at the Lovelace Foundation.

To provide values approaching equilibrium concentration at an early stage of rebreathing, a known quantity of  $\text{CO}_2$  (4-6%) is added to the oxygen in the rebreathing bag. The ideal initial mixture is still being investigated. Rebreathing at a controlled rate is permitted for about 10 breaths, or less than 15 seconds (the approximate recirculation time). With each expiration into the bag, the expired  $\text{CO}_2$  concentration in breath  $n$  will equal that in the succeeding breath  $n + 1$ . Thus, if the  $\text{CO}_2$  in breath  $n$  is plotted against the  $\text{CO}_2$  in breath  $n + 1$  the resulting plot can be extrapolated to meet the identity line (Figure 2) from the points obtained during the period prior to equilibration. The point of meeting represents a very close approximation of the concentration of  $\text{CO}_2$  at equilibrium. In point of fact, the actual  $\text{CO}_2$  curve from the rebreathing maneuver is an asymptote whose intercept with the identity line is infinity. Since there is a constant production of  $\text{CO}_2$  in the body, the  $n + 1$  breath will never have the same amount of  $\text{CO}_2$  as the  $n$  breath. Under exercise the difference will be even greater but the actual quantitative difference is sufficiently small that the extrapolation procedure can be applied. Thereafter,  $\text{CO}_2$  content can be derived from a dissociation curve and the Fick equation completed.

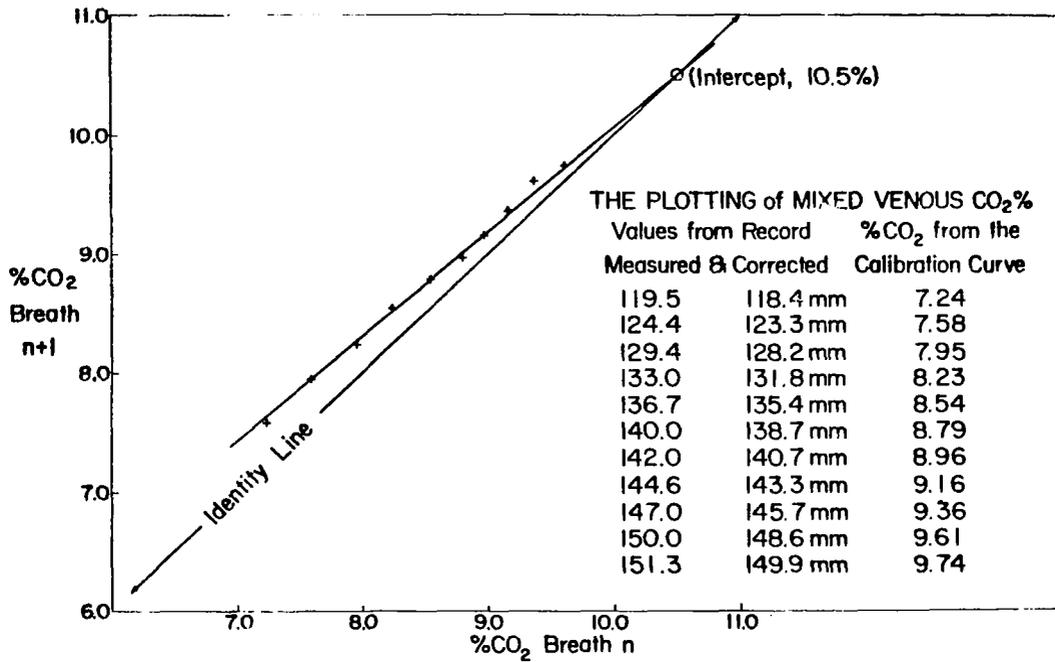


Figure 2  
 The plotting of mixed venous CO<sub>2</sub>%. This shows the method used to extrapolate a CO<sub>2</sub>% level from which the P<sub>VCO<sub>2</sub></sub> is calculated.

Source: Garza, (124)

Garza ( 124 ) draws attention to the errors that can arise in the use of this method and notes the requirement for steady state conditions, accurate calibration and precision, rapid response  $\text{CO}_2$  measures, care in protocol, and positioning of subjects. He refers to the work of Dubois and his colleagues ( 87 ) who showed that lung tissue and fluids have the capacity to absorb evolved and inspired  $\text{CO}_2$  and that the movement of stored  $\text{CO}_2$  into the lung fluids causes a more slowly rising  $\text{P}_{\text{CO}_2}$  in the alveolar air than would be predicted from the volume of air in the lungs and the rate of  $\text{CO}_2$  output. Nevertheless, the reproducibility of the results obtained in Luft's laboratory, and comparison with other methods of obtaining cardiac output indicates the applicability of the method. Table ( 3 ) shows a comparison with other methods ( 124 ).

TABLE 3

Method	Position	Cardiac Index (mean)
$\text{CO}_2$	Supine	3.50 liters/min/m <sup>2</sup>
	Seated	4.89 liters/min/m <sup>2</sup>
Direct Fick	Supine	3.62 liters/min/m <sup>2</sup>
Foreign gas	Seated	4.80 liters/min/m <sup>2</sup>

In a more recent study by Klausen ( 173 ), a comparison was made between cardiac output determined by  $\text{CO}_2$  rebreathing and by the acetylene technique of Grollman ( 142 ). The values obtained by the two methods were highly comparable, with a standard deviation over all experiments of  $\pm 7.3\%$ , and were of the same magnitude as those obtained by others with dye-dilution or direct Fick techniques.

Although originally sampling of the rebreathing bag and measurement of CO<sub>2</sub> concentration by the Scholander method were required, the use of an on-line rapid response CO<sub>2</sub> measuring device provides highly satisfactory results. The technique would be applicable to space laboratory use because of its inherent simplicity, reliability, and reproducibility, and minimal violation of the subject.

Besides oxygen and carbon dioxide, other gases have been used as reference materials. The amount of an introduced gas which is absorbed is dependent on the pulmonary blood flow; hence if its solubility in blood is known and its rate of absorption is measured, the cardiac output can be calculated. Several gases, including nitrogen, nitrous oxide, ethyl iodide, ethylene, and acetylene have been used for this purpose. Of these, the acetylene technique of Grollman (142) has probably been the most popular, but also suffers from problems arising from recirculation and absorption in the lung fluids. In any event, the use of foreign gases in space laboratory conditions would seem inadvisable both from the point of view of possible atmospheric contamination and because of difficulties in storage.

#### Dilution methods

Dilution methods of determining cardiac output involve a modification of the Fick principle first suggested by Stewart (317), and modified by Hamilton and his associates (150). The methods depend on the fact that if a material is introduced into the blood stream, and is uniformly mixed, the concentration becomes dispersed and can be represented as a function of time  $c(t)$ , where  $c$  is the concentration, and  $t$  the time. Moody and his colleagues (227) analyse the resulting relationship as follows:

In any time,  $\Delta t$ , the amount of dye passing the sampling point is:

$$F c(t) \Delta t, \text{ where } F = \text{flow}$$

and since the whole of the dye,  $I$ , will eventually pass the sampling point,

$$I = \int_0^{\infty} F c(t) dt \quad (9)$$

If the flow,  $F$ , is constant, then :

$$F = \frac{I}{\int_0^{\infty} c(t) dt} \quad (10)$$

If the flow and the concentration are independent of the time interval, the cardiac output in liters per minute can be represented in the more common form of the equation:

$$F = \frac{60 I}{ct} \quad (11)$$

In practice, a dye or other indicator is injected into the right heart or the venous system and its timed course of appearance and build-up is monitored in the arterial blood. The injected substance begins to appear after a delay of 6 to 15 seconds, builds up to a peak concentration and rounds off. After an apparent exponential descent for a time, a secondary build up occurs as recirculation begins. The occurrence of recirculation provides a problem in determining the actual time concentration of the material in its first circulation. Advantage, however, is taken of the apparent exponential descent of the curve, and by extrapolating the descending limb of the curve linearly on a semi-log plot of concentration versus time a measurable area can be defined (Figure 3) from which the necessary calculations can be made.

Doubt has been expressed as to whether the descending limb of the curve actually is exponential. Experiments with analog models of the circulation have shown that the curve becomes exponential only when a mixing chamber is incorporated in the analog <sup>(149)</sup>. As compared with direct Fick methods, however, the results have shown an acceptable agreement, which tends to indicate that any deviation from a true exponential decay is not sufficient to negate the use of the method.

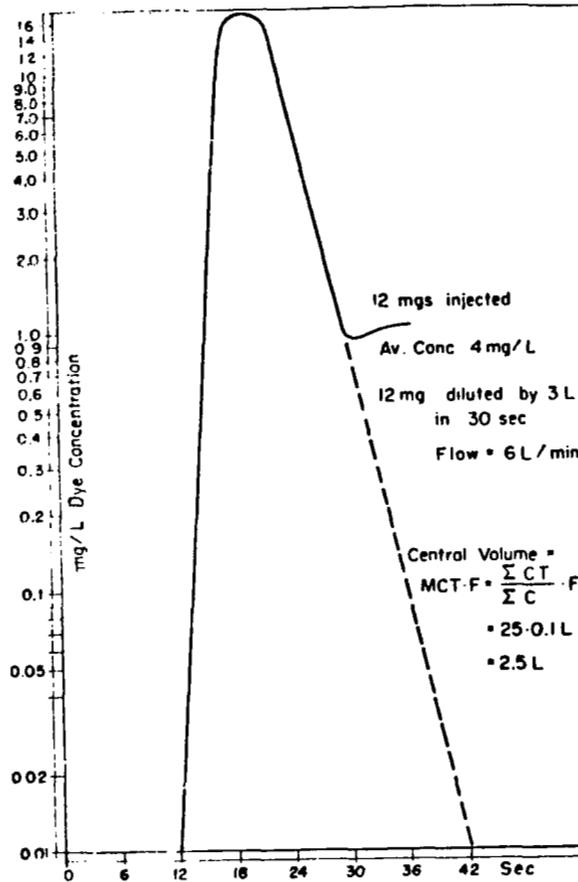


Figure 3

Changes in arterial dye concentration after injection into a vein. Cardiac output is calculated from data given on the figure.

Source: Hamilton ( 146 )

Sampling procedure has provided a continued problem. Early methods required samples of arterial blood at one-second intervals for analysis of dye content. Development of the arterial cuvette, which allows a continuous analysis of the blood passing through it, reduced the sampling problem considerably, but created new problems in dye selection and in blood loss. The cuvette contains a light source and a photoelectric cell, the output of which varies according to the amount of absorption of light that takes place by the blood and by the dye carried by the blood. The cuvette, however, has certain disadvantages. Distortion of the dye curve may result from the passage of blood through the connecting polyethylene tubing, although this can be reduced by maintaining a flow rate greater than 0.71 ml/sec<sup>(182)</sup>. Stray light may enter the photoelectric cell; the response of the recorder may not be linearly proportional to the dye concentration throughout the entire range, and drift of the recorder may occur. In addition, there are limitations inherent in the photometry of blood, largely due to its heterogenous character, with a tumbling mass of red cells, a clearer peripheral area, and streaks of protein stained by dye<sup>(80)</sup>.

The requirement to distinguish between the absorption characteristics of hemoglobin and dye raises problems in dye selection, compounded by the requirement to ensure minimum toxicity, and ideal diffusibility. Numerous materials have been used, and one of the more popular dyes is Evans blue or T-1824<sup>(76)</sup>. It is relatively non-toxic but very slowly excreted. Tissue staining may last for several days following a dose greater than 50 mg<sup>(253)</sup>. Use of this dye is further complicated by the fact that its absorption spectrum, maximum at 620 to 640 millimicrons, is similar to that of reduced hemoglobin and necessitates continuous oxygen administration during recording. This problem can be overcome by utilizing a dye such as indocyanine green ("cardio-green") the sensitivity of which is minimal at about 800 millimicrons and maximal at about 925 millimicrons. This dye, however, is removed from the circulation so rapidly that some workers, at least, maintain

that proper calibration of the dye curve cannot be obtained ( 323 ). Certainly one of the most suitable dyes is Coomassie blue ( 324 ) which is a water-soluble compound of low toxicity with a half-life, in the circulation, of 15 to 20 minutes, and maximal absorption sensitivity around 580 millimicrons, which reduces its interference by hemoglobin.

Procedures involved in the calculation of cardiac output from dye curves are cumbersome and tedious. In essence they require transfer of the data from the first portion of the curve onto semi-log graph paper, extrapolation of the descending portion of the first curve to meet the base line, planimetry of the resulting area, extraction of a value representing mean concentration, and calculation of the flow which would provide such a concentration. Moody et al., ( 227 ) described a method whereby an electronically generated curve could be matched against the dye concentration curve. The results can be read in terms of cardiac output and mean transit time. Various commercial instruments are now available which reduce much of the labor involved and are inherently more accurate than hand calculation methods.

The above noted dye techniques require arterial puncture, with discrete or continuous arterial sampling. These factors reduce their applicability for use in manned space operations. To overcome this difficulty Wood and his associates at the Mayo Foundation have been using an ear cuvette which measures changes in absorption of light transmitted through the ear lobe. Although this method has met with some controversy, it has been used with considerable success by Wood and his colleagues. Reed and Wood ( 267 ] describe refinements in the technique using a dichromatic earpiece densitometer containing two photocells, one of which is sensitive to dye (indocyanine green) and one which is insensitive to dye. The use of a dichroic mirror allows both cells to view the same optical pathway of the ear. Both cells are approximately equally reactive to changes in transilluminance of the ear caused by changes in blood content, hematocrit, or other non-specific effects, but one is sensitive to dye, the other not. Both cells are

relatively insensitive to changes in oxygen saturation of the transilluminated blood. Compensation for non-specific changes in the ear unrelated to dye is obtained by using these cells in reverse polarity to each other. The "bucking" of the detecting cell against the compensating cell provides a stable baseline from which the end-tail method of calibration of a dye such as indocyanine green can be measured even though the removal rate of dye from the arterial blood is rapid.

To determine cardiac output from the earpiece densitometer a calibration factor is required. Originally this was obtained by independent analysis of an arterial sample, or averaged arterial samples. Using this method Reed and Wood found no systematic difference between cardiac output determined by the earpiece and by arterial cuvette, although the standard deviation in the former was large ( 31% ). They also showed that an acceptable calibration factor could be obtained from venous rather than arterial samples, with, in this case, a systematic underestimation of 7%. They further went on to show that once the earpiece has been calibrated by blood sample in terms of cm. deflection of the galvanometer per mg. of dye per liter of blood, any further calibration could be made from a factor related to the amount of blood actually being transilluminated. This measure can be obtained by measuring the difference in output of the infrared cell when the ear is in the normal blood containing state and when the transilluminated portion is rendered essentially bloodless by inflating the pressure capsule on the apparatus to over 200 mm Hg.

Thus, after pre-calibration of the instrument, it is possible to obtain a measure of cardiac output without arterial puncture and without venous puncture other than to inject the dye. It is emphasized that a high degree of familiarity with the method is necessary and that the standard deviation of the results is large, but it is believed that allowing for further development, the technique may have application in a manned space laboratory. The earpiece cuvette, however, suffers from the same disadvantages as the arterial cuvette. In addition, head movements may

cause irregularity of the base line, and vasodilation must be ensured by heat or a rubifacient, otherwise vasoconstriction may interfere with registration of the dye curve ( 253 ).

### Electrical conductivity

The original application of the Stewart principle by Stewart in 1897 involved the incorporation of a segment of an artery into a Wheatstone bridge. Injection of salt solution changed the electrical conductivity of the artery which was signalled by the automatic ringing of a bell. At this time the arterial flow was diverted into a tube for sampling. Although accurate in principle the technique is not very practicable. White ( 341 ) modified the method for continuous recording of conductivity by devising miniature conducting cells which could be inserted into an artery by way of a modified hypodermic needle. Using this system White successfully measured cardiac output in isolated preparations and intact dogs. There is no record of its having been used in man and it also does not now appear very acceptable for space use.

### Thermal dilution methods

The use of temperature change in the blood flow has been suggested as another modification of the Stewart principle. One such approach is that of Fegler ( 98 ) who calculated cardiac output from the temperature difference between saline at room temperature and at the equilibrium temperature which developed after injection of the saline into the right atrium. The theory is based on the assumption that heat exchange takes place only between the saline and the blood. Doubt, however, has been cast on the adequacy of the mixing that takes place, and it has been suggested that heat exchange also takes place in the lungs, although the possibility of the latter is minimized by Webb and Crocker ( 334 ). Using very careful techniques and calculating for all potential sources

of heat exchange, Goodyer and associates have shown a close correlation between the thermodilution method of obtaining cardiac output and the direct Fick in animals. However, the method is complex and currently requires cardiac and arterial catheterization. Consequently, it would not be suitable for use in space.

Another form of thermodilution technique is being currently examined in Paul Webb's laboratory ( 334 ), in which attempts are being made to apply a "slug" of heat to an artery by way of high intensity ultrasound and thereafter measuring the change in temperature by a thermistor in the nose. So far the results have been somewhat discouraging but the principle appears to present a hopeful potential.

#### Radioisotope methods

The use of injected radioisotopes as reference material began with Prinzmetal and his associates in 1949 ( 260 ). The most commonly used material has been human serum albumin tagged with  $I^{131}$  (RISA). The method depends fundamentally on utilization of the Stewart-Hamilton principle to compute the cardiac output from measured concentration of the RISA. Two main approaches have been made to obtain the measurement. MacIntyre and his associates ( 202 ) utilized a method whereby the radioactive count rate at peak concentration was obtained from a sample of arterial blood withdrawn by way of a tube coiled round a rate counter. Calibration in terms of concentration was achieved by obtaining a further count rate when equilibrium had been reached and matching that against a dilution of the injected indicator.

To avoid the necessity of withdrawing arterial blood, Shipley and his associates ( 300 ), Huff and his associates ( 160 ), and others, extended the work of Prinzmetal by using scintillation equipment with careful positioning over the precordium, and eventually with more refined collimation of the detector head. With the precordial equipment, calibration again offered difficulties. These have been tackled in a manner somewhat similar to the computations required in determining dye concentration.

The average intensity of radioactivity is obtained from a semi-log plot of intensity versus time of the first portion of the radioactive curve. If the final concentration of the curve is determined when the RISA is uniformly mixed throughout the intravascular space ( 10 - 20 min), the average intensity during registration of the curve compared to the intensity at equilibrium represents that portion of the blood volume which must have traversed the site of the detector during the primary circulation. If the blood volume is known, the flow rate per minute may be calculated as follows:

$$F = \frac{BV \times c_e \times 60}{c_{av} \times t} \quad ( 12 )$$

where

- F = flow (cardiac output)
- BV = blood volume
- c<sub>e</sub> = concentration of isotope at equilibrium
- c<sub>av</sub> = average concentration of isotope in primary circulation
- t = time of primary circulation in seconds from extrapolated plot

These relationships have been presented by MacIntyre and his associates ( 204 ), Huff and his associates ( 160 ), and Schreiner and his associates ( 290 ). In a further analysis, MacIntyre and his group ( 203 ) point out that the blood volume measured is not necessarily the circulating blood volume as usually calculated by dilution methods, but is actually the volume of dilution of the injected material at the time when the sample was withdrawn. In most cases, after a 10 minute mixing time this volume would approximate the total blood volume.

A problem arises from difficulty in determining the actual downslope which should be extrapolated. The curve obtained from a precordial detector normally presents in two peaks, representing the outflow from the right and left ventricles respectively, but including elements of pulmonary and coronary flow. However, the first part of the left ventricular curve and the last part of the right ventricular curve are super-

imposed and it is not always possible to find a downslope of the right heart curve which can be extrapolated. Where a suitable downslope is not obtainable the method is invalidated.

Doubt has been case on the validity of the technique because of differences in results obtained with varying positions of the detector, varying collimations, and differences in "focussing" distance that may occur with chest movement during respiration. In particular, Carter and her associates ( 56 ) in experiments with dogs found that an uncollimated precordial scanning technique gave results averaging 1.8 times greater than those obtained by continuous counting of a peripheral artery; with a collimator there was a closer approximation. Changing the position of the detector on the precordium gave results which produced variations up to twice control.

Despite these findings, good correlations have been found with direct Fick and arterial methods in other circumstances and the method has received considerable acceptance. In a study of 44 subjects Schreiner et al., ( 290 ) found the mean precordial value of the stroke index was 3.53 liters/min/M<sup>2</sup> and the arterial value 3.46 liters/min/M<sup>2</sup>; while in 25 instances the mean values for precordial, arterial, and Fick methods were 2.97, 2.91, and 3.01 liters/min/M<sup>2</sup> respectively. Furthermore, the estimated standard deviation between duplicate measures with the precordial technique compared favorably with that from the Fick.

The use of radioisotope techniques has much to commend it in space operations. The application depends upon effective compromises among factors of detector sensitivity and positioning, dosage of radioactive materials, collimation, and sampling rates. It has the advantages of simplicity in execution, rapidity, and avoidance of arterial puncture or catheterization. At the same time the instrumentation is complex, the repeated exposure of astronauts to radioactive materials is inadvisable, and the storage of the materials would present problems. It would consequently seem unwise to consider it a method of priority. (See Section III).

As an addendum, it might be noted that Cournand and his colleagues ( quoted by Hamilton ( 146 ) ) have made precordial measures of radioactive krypton injected intravenously. Since the krypton is highly diffusible it is eliminated in the lungs before reaching the left ventricle and consequently provides a clear picture of concentration in the right heart only. Unfortunately the half-life of  $K^{85}$  is so short that storage for space operations would not be practicable.

### Methods involving measures of cardiac kinetics

#### Ballistocardiography

Concepts governing the use of ballistocardiography for other aspects of cardiac evaluation are considered elsewhere in a general discussion of cardiac kinetics.

Beginning with Starr and his colleagues ( 313 ) with the high frequency ballistocardiographic table, several workers have developed formulae relating events of the ballistocardiographic trace to the stroke volume ( 236, 143, 174, 276 ). It is not proposed to discuss and derive the individual formulae which are highly complex and include constants to take into account factors such as peripheral resistance, systolic ejection time, pulse wave velocity, age, body dimensions, table coupling, etc., as well as measurements of amplitudes and time dimensions of the trace. Formulae will be found in the original papers quoted.

The method depends on equating the acceleration forces developed by the mass of the blood ejected from the right and left ventricles with the acceleration forces developed by the recoil of the body and modified by the motions of the heart and vasculature. From these equations, calculations can be made to provide values representative of stroke volume.

In a review of the field, Hamilton ( 146 ) points out that there is no simple quantitative relationship between the recorded trace and the forces

of ejection from which the stroke volume can be derived. In the first place the recoil which is recorded is responsive not to the steady flow but to the acceleration of that flow, as can be demonstrated by experiments with models. Furthermore during systole there are many forces generated at the same time, some of which are contrary to each other and tend to cancel out. As Rushmer ( 283 ) notes, the blood ejected from the two ventricles moves simultaneously in several directions after leaving the heart, and its energy is imparted vectorally to the body at every turn. In addition, Hamilton ( 148 ) has shown that accelerative forces in the venous return contribute to the total picture.

Thus, it would appear that although correlations have been shown between stroke volumes derived by ballistogradiographic methods and those by Fick or modified Fick methods ( 237, 313 ) the respective formulae tend to be somewhat empirical and have a doubtful inherent validity, which, however, does not render them less useful.

With respect to manned space laboratories, it would not seem reasonable to justify inclusion of ballistocardiographic apparatus solely for the purpose of performing measures of cardiac output. However, if it is deemed advisable to include such apparatus for other purposes, cardiac output determinations could readily be made. Under those circumstances, however, it would seem necessary to undertake a comparative study to determine which of the various methods of calculation would provide the most reliable data.

### Precordial kinetics

Very little attempt has been made to correlate records of precordial traces with determinations of stroke volume. As will be noted in the section on cardiac kinetics, Agress ( 4 ) utilizes measurements of the ejection phase ( $J_2-L$ ) of the precordial vibrocardiogram to determine relative changes in stroke volume. However, because of considerable extraneous variation in the wave form of the vibrocardiogram, and because of some doubt as to what manifestation of energy the trace is actually reflecting, controversy has arisen over the interpretation of

the stroke volume measure. Should the vibrocardiogram be used as a routine measure in space operations it will of course be advantageous to make the calculation if only for comparative purposes.

Measurement of precordial acceleration appears to show more potential. In an unpublished study in which 12 subjects were stressed by exposure to step fashion to hypoxia at 25,000 feet in an altitude chamber, Proper and Nevison showed a linearly proportional relationship between the amplitude of the "E" peak of the accelerogram and the increase in stroke volume occurring with hypoxia. Under the conditions of the experiment it will be observed from Figure 4 that as a stroke volume rose from 52 to 106 cc with increase in altitude, the amplitude of the accelerogram trace doubled from an arbitrary value of 1 to an arbitrary value of 2. It must be noted here that stroke volume in this case was calculated from the displacement ballistocardiogram formula of Klensch, and was not determined by Fick or dye procedures. Thus, the relationship must be considered relative. With quantification of the accelerogram trace, such as would be possible with an accelerometer calibrated in terms of g versus stroke volume, it would seem feasible to develop a technique for determining stroke volume from the accelerogram tracing. If, as is recommended in the section on cardiac kinetics, accelerogram tracings are employed in manned space operations, the potential of obtaining stroke volume determinations therefrom would be a useful dividend.

#### Methods involving ultrasonic techniques

While the use of ultrasonic methods of determining blood flow and cardiac output has proven of significant value in animals, the technique currently demands implantation of ultrasonic generating and sensing devices. Consequently no application to man is seen for the near future. A brief review, however, is probably in order to permit evaluation of potential developments. Useful studies of ultrasonic physics in

- Precordial Accelerographic Tracing - Amplitude
- Stroke Volume - Displacement Ballistocardiograph (Klensch).

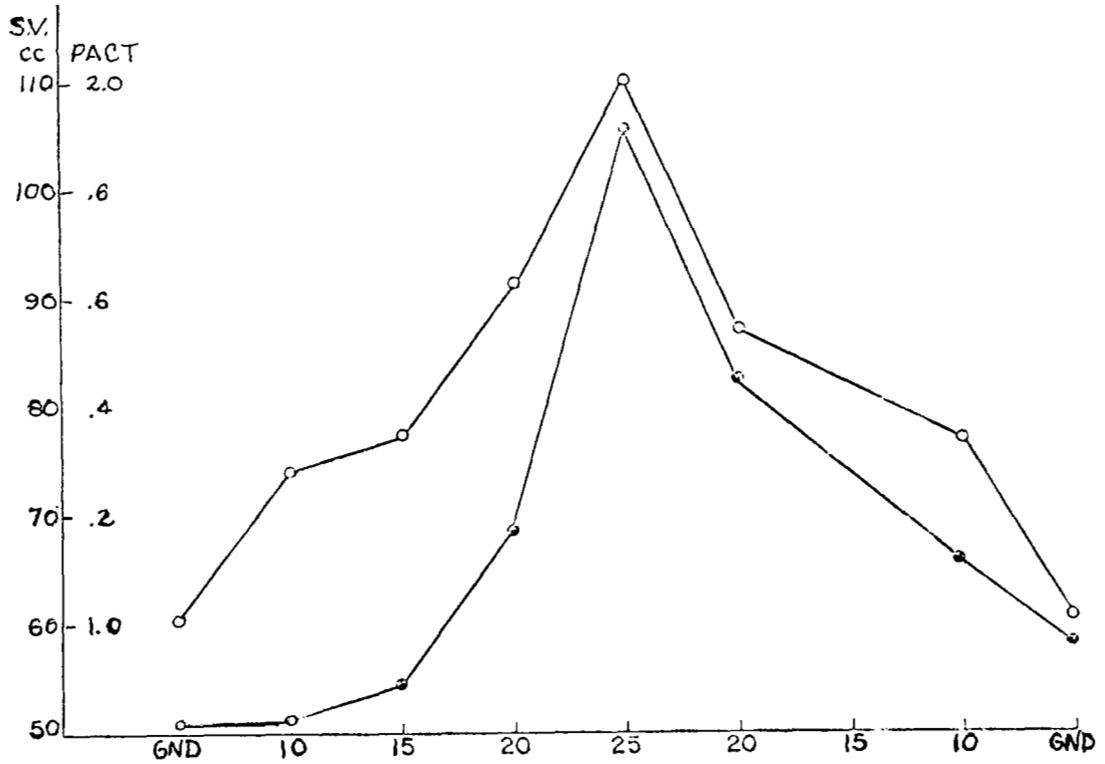


Figure 4

Source: Proper and Nevison

(Unpublished report)

relation to biology have been made by Nelson et al., ( 235 ), Edler et al., ( 93 ), and Joyner and Reid ( 166 ).

Ultrasonic frequencies currently employed in biological investigation and treatment range from above 20 kilocycles per sec (Kc) to around 1 million Kc. For investigative and diagnostic purposes the frequency is commonly of the order of 700 - 1000 Kc. At these frequencies ultrasonic waves tend to behave more like light waves than sound waves. Like audible sound waves they travel through a conducting medium as longitudinal vibrations with alternate compression and rarefaction within the medium, but travel with considerably less scatter. Like light waves, ultrasonic waves may be reflected and refracted under suitable conditions, and may be focussed by an acoustic lens.

The velocity of sound in a medium is a constant dependent on the characteristics of the medium, while the transmission in a medium is dependent upon the acoustical impedance, which in turn is related to the frequency of the sound, the velocity, and the density of the medium. When a sound wave travelling through an acoustically uniform medium reaches an interface with a medium with a different acoustical impedance, a greater or less degree of reflection of the sound will occur dependent on the magnitude of the difference of the impedance. There is a large difference between the impedance of a generating crystal, the impedance of air, and the impedance of different tissues. These differences lead firstly to the necessity of having a coupling medium, generally water or oil, between the generator and the tissue, and also to the difficulty of transmission of ultrasonic waves into organs surrounded by air, such as the heart.

The most commonly used generator of ultrasonic waves in biological investigation is the piezoelectric crystal. These crystals have the ability to become electrically charged on opposite surfaces when subjected to pressure. Conversely, such a crystal will undergo vibration at very high frequency when opposite sides are subjected to an alternating electric field.

With these and other transducers, ultrasonic waves of different intensity and frequency have been applied to tissue in vivo and in vitro for investigative, diagnostic, and therapeutic purposes. The whole field of ultrasonics in medicine is discussed by Edler and his colleagues ( 92 ) who have pioneered the field in Sweden. Notable exponents in this country are Howry at the University of Colorado, Wild in Minneapolis, and Reid and Joyner at the University of Pennsylvania, while much work has been done in Rushmer's laboratory in the measurement of blood flow.

Several different techniques have been used to determine blood flow. Rushmer, Franklin, and Ellis ( 284 ) attached crystals to each side of the left ventricle of an animal and obtained a virtually continuous record of change in diameter of the heart chamber from which output of the ventricle could be calculated. Other devices are based on ultrasound transit times. Franklin and his associates ( 110 ) in Rushmer's laboratory attached a transducer to the aorta in such a manner that the signal was transmitted diagonally back and forward across the flow. The difference in transit time between signals travelling with and against the flow provided a measure of flow rate. Out of the same laboratory Franklin et al., ( 109 ) devised a flow meter which utilized the back-scattering of ultrasound by the moving stream to measure a Doppler frequency shift which also provided a measure of flow rate.

All these methods utilize implantable transducers which can be left in situ and used for continuous and repetitive measures, but, of course, because of the surgery involved, they are not at this time considered applicable to man.

External ultrasonic techniques are used extensively in diagnosis. The simplest (the "A" scan) presents a sonar type of display whereby a reflected echo is shown on a time scale proportional to the distance between the origin and the reflecting surface. It is used among other purposes to determine shifts in the midline of the brain. In the "B" scan technique, echoes are displayed as dots; by moving the transducer around the part to be examined in both a horizontal and circular motion the echo-produced dots are scanned in a two-dimensional dis-

play to produce a somagram which represents the underlying structure. Various other complex compound scans are employed. The echo-cardiogram was developed by Edler and Herz ( 93 ) and is described in Edler's comprehensive review ( 92 ). With the transducer suitably placed on the precordium, signals attributable to heart motion can be obtained. Pulsations can also be observed when the beam is directed to the aortic arch via the root of the neck. More recently work has been undertaken by Franklin and others to obtain measures of aortic flow by external scan. Although still experimental the approach seems very promising.

Ultrasonic investigative methods are still in a very early stage of development. It is possible that in time reliable external techniques will become available for the determination of blood flow rates and cardiac output.

#### Methods involving impedance plethysmography

The use of impedance plethysmography in the measurement of segmental volumes depends upon the relationships defining the electrical volume of a volume conductor, and on the concept of parallel resistive impedances introduced by Nyboer ( 239 ).

The volume of an electrical conductor can be defined as follows: (Nyboer ( 240 )):

$$V = \rho \frac{l^2}{R} \quad (13)$$

where

V = volume (ml)

$l^2$  = length (cm)

$\rho$  = specific resistivity (ohm centimeters)

R = resistance (ohms)

Using models, Nyboer ( 239 ) showed that the physical change of volume over a limited range within a cylindrical elastic membrane

(rabbit aorta) is directly proportional to the change in electrical conductance of its electrolyte contents, if measured between fixed points in the longitudinal axis of the cylindrical system. Expansion of a blood vessel within a given length of body segment, such as an arm, results in an increase in cross section and volume. The material (blood) expanding a segment has a different specific resistivity than the surrounding material. The effective relations of the volume change can be expressed as those of an added resistance in parallel to the resistance of the other tissues.

According to the theory of parallel resistance,

$$R_{\text{total}} = \frac{R_1 \cdot R_2}{R_1 + R_2} \quad (14)$$

Rearranging,

$$R_2 = \frac{R_1 \cdot R_{\text{total}}}{R_1 - R_{\text{total}}} = \frac{R_1 \cdot R_{\text{total}}}{\Delta R} \quad (15)$$

When radio frequency signals ( 50 - 120 kc ) are passed into the tissues, the resulting impedance is almost entirely resistive (Nyboer <sup>( 240 )</sup>) and the equation expressing the pulse volume can be written as:

$$R_b = \frac{R_n \cdot R_o}{\Delta R} \quad (16)$$

where

- $R_b$  = calculated parallel resistive impedance equivalent to given pulse volume
- $R_n$  = new resistive impedance during segmental distribution of blood pulse
- $R_o$  = original segmental resistive impedance

The calculated value of  $R_b$  can be incorporated into Equation 13 to determine the change in volume (  $\Delta V$  ) after measuring length (  $l$  ) and using a previously determined specific resistivity (  $\rho$  ), usually considered to be 150 ohm cm at body temperature.

These relationships have been verified by Allison ( 7 ) and Allison and Nyboer ( 12 ) in carefully controlled models. Using an ionic fluid in a graduate jar with a constant hindrance to outflow, and also with an expansible segment in the outflow tract, they measured the changes in resistive impedance resulting from changes in volume, and showed that: (1) the resistance in an electrolyte solution to a constant current varies directly as the length between the detecting electrodes when the cross-sectional area is constant, (2) the resistance varies inversely as the cross-sectional area when the length is constant, (3) a new ionic volume increasing the cross-sectional area acts electrically as though in parallel with the non-expanded segment.

In practice ( 8, 9, 10, 11, 12 ) to determine volume in a segment, an oscillator feeds a 100 kc current to a buffer amplifier stage. The buffer is coupled through a transformer to a modified Kelvin double bridge of which the segment is a part. The signal is introduced to the segment through a pair of outer electrodes and detected between two inner electrodes. A two-electrode system can be used for both input and output but it is not so satisfactory due to inclusion of electrode contact resistance at balance. Impedance is measured as an imbalance of the bridge, the output of which is amplified and led to a recorder. On completion of the record, electrode leads are electrically switched to a decade substitution box. Null balance by substitution provides a measure of the impedance between the inner electrodes and expresses the gross resistive impedance of the system ( $R_o$ ). 1 ohm and 0.1 ohm standards are also recorded for calibration purposes.

In measuring the change in resistive impedance occurring with change in volume it is necessary to bear in mind that the pulse volume contains systolic and diastolic components separated by the dicrotic notch. During both systole and diastole, drainage is taking place. From the beginning to peak of systole, arterial inflow exceeds venous outflow. The peak of systole represents the maximum arterio-venous volume exchange. Following closure of the aortic valve, represented by the occurrence of the dicrotic notch, outflow from the segment occurs as venous run-off. To

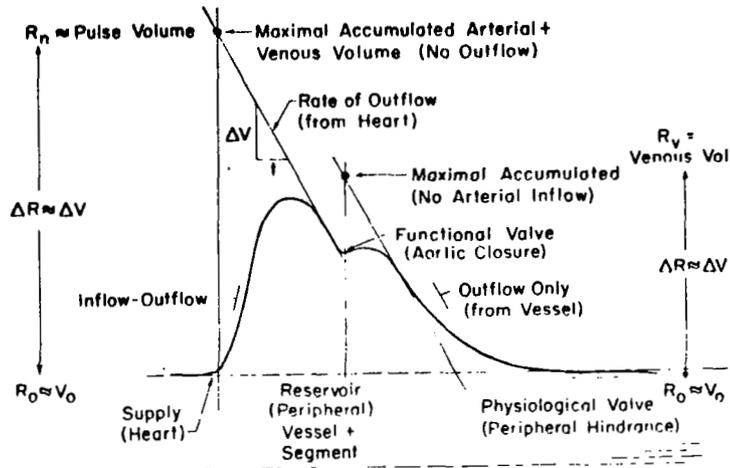


Figure 5

#### Systolic and Diastolic Pulse Volume Components

Peripheral Pulses depend on a blood supply, a reservoir and variable physiological hindrance to outflow. From the beginning to peak of systole, arterial inflow exceeds venous outflow. The peak of systole represents the maximal arterial-venous volume exchange. Following closure of the aortic valve (dicrotic notch) outflow from the segment is represented as venous run-off. Extrapolation of the systolic slope to beginning systole predicts the maximal volume delivered to the segment for one cycle and corrects for venous run-off (9). Extrapolation of the end-diastolic slope to beginning of diastole predicts the maximal venous volume at peak systole.

Source: Allison ( 8 )

allow for venous drainage when making a measure, the systolic down-slope of the curve before the dicrotic notch is extrapolated backwards to the point representing the beginning of systole, as suggested by Nyboer and illustrated in Figure 5 from the work of Allison <sup>( 11 )</sup>. The beginning of systole is obtained from a concurrent ECG, phonocardiogram, or vibrocardiogram. The validity of this extrapolation procedure has been verified in the model experiments previously noted <sup>( 7, 12 )</sup>. The calculated flows agreed very closely with the actual measurement of the volume flow in the graduate jar. Patterson and his associates <sup>( 250 )</sup> from the University of Minnesota use a different measure of the same duration, extrapolating forward along the upslope from the onset of systole to the closing of the pulmonary valves.

So far consideration has centered on the general aspects of impedance plethysmography, and in this field the leading exponents have been Nyboer from Wayne State University, Allison from the Lovelace Foundation, and Kubicek and his associates from the University of Minnesota. Application of the technique to the determination of cardiac output raises other considerations. When input electrodes are placed across the base of the neck and at a level between the subcostal and intertubercular planes, and when detecting electrodes are placed 30 cm apart across the crest of the shoulders and the level of the diaphragm, the record shows excursions synchronous with respiration, and also smaller excursions synchronous with the cardiac cycle. Pulses are similar in form to peripheral pulses, but are 180° out of phase with peripheral pulses, indicating increased resistance during systole, unlike peripheral pulses which demonstrate decreased resistance following systole. Electrodes are placed on the posterior thorax to minimize change in distance between the electrodes that might occur with respiration. Breathholding abolishes the excursions associated with respiration.

Patterson and his associates <sup>( 250 )</sup> undertook a series of experiments, which are also reported in part by Kinnen et al., <sup>( 70 )</sup> to determine if in fact the lesser changes in impedance observed reflect pulses of pulmonary blood flow representative of cardiac output. Using

a fixed electrode, a small movable electrode, and catheter electrodes in the carotid artery, jugular vein, aorta, heart, esophagus, trachea, and large bronchi, they determined the current flux distribution in the thorax. They showed that impedance decreased during systole and increased during diastole except when electrodes were placed over the heart. With electrodes in the standard position, the rapid decrease of impedance during systole suggested movement of blood into the pulmonary volume or into the large vessels. Since, however, the major current flow was to the right of the spine and the large vessels are located to the left, the pulmonary blood flow would appear to provide the main path. This was confirmed by measuring the total impedance of a portion of a dog's aorta (3100 ohms), and comparing it with the total impedance measured externally over the same portion (5 ohms). On the basis of their experiments they concluded that the preferred current flux path in the thorax with a 100 kc excitation signal is the lung blood volume, and the impedance wave from may be reflecting the pulmonary blood volume changes.

They then extended their experiments ( Kinnen et al ( 170 ) ) to measure cardiac output on 5 subjects before and immediately after exercise, using Bonjer's ( 39 ) form of the impedance equation which gives a value for change in volume, as follows:

$$\Delta V = \rho(L/Z)^2 \Delta Z \quad (17)$$

It might be noted that this equation calls for measure of total impedance (Z) whereas in point of fact they were measuring resistive impedance. However, with this technique they showed a close relationship between cardiac output measured by plethysmography and representative cardiac outputs on 50 subjects made by the foreign gas technique and reported by Grollman ( 142 ), with an average difference of 8%. They also showed a close correlation between the O<sub>2</sub> consumption of their subjects and the cardiac output obtained by plethysmography, (r = 0.962).

Allison, who pioneered in this measure, has undertaken numerous determinations in both animals and man. He emphasized, however, that the technique provides a measure of pulmonary pulsatile flow rather than stroke volume. The distinction may seem academic, but Allison argues that once the blood flow leaves the right ventricle and passes into the pulmonary circulation it becomes responsive to factors which affect the peripheral circulation. Thus, for example, during thoracic impedance plethysmography, changes in apparent stroke volume may be observed during extreme respiratory excursions and during Valsalva and Mueller maneuvers (Allison and Luft <sup>( 9 )</sup>). Again, with subjects breathing a gas mixture equivalent to an altitude of 23,000, a 39% reduction in pulmonary pulse volume can be demonstrated (Allison and Luft <sup>( 11 )</sup>). With subjects in the seated position, there is a greater reduction in the lower thoracic segments than the upper although this difference is not so pronounced in the supine position. The same postural dependence is very marked in blood flow in limb segments <sup>( 8 )</sup>. However, with the subject at rest, under stable conditions, the measure can provide a close index of stroke volume.

Comparative analysis of stroke volume in dogs, determined by impedance plethysmography, and a direct Fick method, have been carried out by Allison, the results of which are shown in the following Table (4). These indicate an acceptably close relationship between the two methods. In addition, he has also carried out impedance measurements of cardiac output in man with results which compare favorably with those generally regarded as standard.

For use in manned space missions the method shows considerable merit. The execution is relatively simple; the instrumentation, although electronically complex, is mechanically simple, and can be miniaturized into small weight and volume; the time to accomplish a measure is brief, and the violation of the subject is negligible. At the same time, the method has disadvantages. It will be apparent that there are assumptions in the theory that bear consideration, and it is also a fact that the technique is prone to artifact. The balance of the amplifiers is readily lost and

TABLE 4

	<u>Fick Cardiac Output</u>	<u>Impedance Calculated Cardiac Output</u>	<u>% Diff.</u>
1.	3.090 3.750	3.100 3.200	3.2 14.6
2.	1.23 1.064	1.100 1.100	10.6 3.6
3.	2.710 2.778	2.828 2.744	4.2 1.3
4.	2.930 2.984	2.731 2.395	6.8 2.1
5.	3.090 3.750	3.500 3.600	1.2 4.0
6.	.840 1.11	.810 .910	3.6 1.8
7.	2.51 2.60	2.200 2.300	1.24 1.2
8.	2.98 2.78	2.630 2.730	11.7 18.0

Source: Allison (8)

is affected by movement of the subject and by the presence of other electrical fields. Use of the system is restricted to conditions involving minimal movement. With continued development, however, it should provide a valuable means of making reliable and simple determinations of pulmonary pulsatile blood flow, representative of cardiac stroke volume.

### Recommendations

In making recommendations concerning techniques for the determination of cardiac output in a manned space laboratory it is necessary to bear in mind the limitations previously noted, namely, weight, volume, available skills, violation of subject, weightlessness, available time, confinement, etc., which act to influence a selection.

From the foregoing discussion it is apparent that the most fundamental, reliable, and thoroughly examined method is the direct Fick using oxygen, or its derivative the dye dilution technique using a cuvette and suitable dye, such as indocyanine green or Coomassie blue. Of these two methods, the dye dilution can be performed with less complexity, less discomfort, and less hazard. Thus, excluding the constraints applied by the space cabin environment, the dye dilution technique would seem to offer the most suitable standard method.

Consequently it would seem advisable, that prior to proceeding on a space laboratory mission, all the astronauts concerned should undergo a careful determination of cardiac output at rest and exercise under simulated space flight conditions with the exception of weightlessness. In addition to providing baseline values, this measure, with suitable additional instrumentation, will provide the means of obtaining proportionality constants for application to pulse pressures, empirical tables, ear oximeters, accelerogram traces, etc., and will allow for ground-based comparison and validation of various techniques.

For use in space, it is probably necessary to consider the requirements for two levels, namely, day-to-day evaluation, and routine regular determination.

For day-to-day evaluation it would seem reasonable to accept that accuracy and reliability can be sacrificed for simplicity. For this purpose, the simple relationships between stroke volume and blood pressure would probably suffice as an index of cardiac function. In fact, pulse pressure alone, without any further calculation, might well be considered to provide an adequate index. Should a little more sophistication be deemed advisable, the table prepared by Remington et al., ( 269 ) (Table 2 ) offers a reasonable approximation to stroke volume from blood pressure measurements, particularly if a proportional adjustment is available from the pre-flight dye dilution studies.

For more accurate, reliable, routine determinations of cardiac output under space conditions, it is difficult, if not impossible, at this time to select a technique which has clear-cut advantages over all the others. As has been demonstrated in the foregoing discussion, several acceptable techniques are available, each of which has its advantages and disadvantages. It is still far from clear how favorably one compares with another even in ideal terrestrial conditions, and how much the consistency of the results is affected by the skill of the user and his familiarity with his own favorite technique. More is needed in the way of comparison studies on the ground, but even after adequate objective comparison it will still not be possible to say with certainty which is the most appropriate technique for use in space since the orbital conditions may not only influence the implementation of the technique but could conceivably also modify some of the supposed constant factors on which a given technique is based.

Thus, despite the complexity of execution, and the violation of the subject, it would seem necessary that for the initial experiments the most reliable and accurate technique feasible, namely dye dilution monitored by an arterial cuvette, should be employed to obtain baseline values. A valuable adjunct to the arterial cuvette would be a curve-matching computer presenting a read-out of cardiac output. Thereafter, other potentially acceptable techniques could be tested for routine use against it. As a possible alternative to the dye dilution method, and bearing in mind that it is not acceptable to all investigators, the CO<sub>2</sub>

rebreathing method would provide much more simply and with considerably less subject violation, results which are probably as reliable as those from dye dilution.

Subsequent to, or in some cases, concurrent with determination of these baseline values, other potentially useful techniques can be evaluated. These could include impedance plethysmography, dye studies using an ear oximeter with and without arterial calibration, radioactive isotope methods, and methods of x-ray cardiometry. As mentioned in the earlier text, ear oximetry, in skilled hands, has much to commend it, particularly if no arterial puncture is required, and merits investigation in orbital conditions. Isotope methods, with carefully controlled protocol, produce consistently reliable results but suffer from the handicap of difficulty in storage, radiation exposure to the subject, and the requirement for sophisticated instrumentation. X-ray cardiometry similarly necessitates radiation exposure and demands highly sophisticated equipment; if the latter is available for other purposes, however, the technique should be investigated.

A potentially valuable technique would appear to be impedance plethysmography, and it might well be used in conjunction with dye dilution in the initial experiments. In addition, the possibility of quantifying cardiac accelerography has been mentioned, to provide at least a relative value for stroke volume, while if ballistocardiography is going to be undertaken for other purposes, incidental calculations can be made from the trace. Ultrasonic methods, particularly those being developed by Rushmer's group, should be borne in mind for possible future application, while the thermal ultrasonic technique of Webb may yet prove useful. In all cases, however, it is essential that the orbital investigator be thoroughly familiar with the techniques he is using.

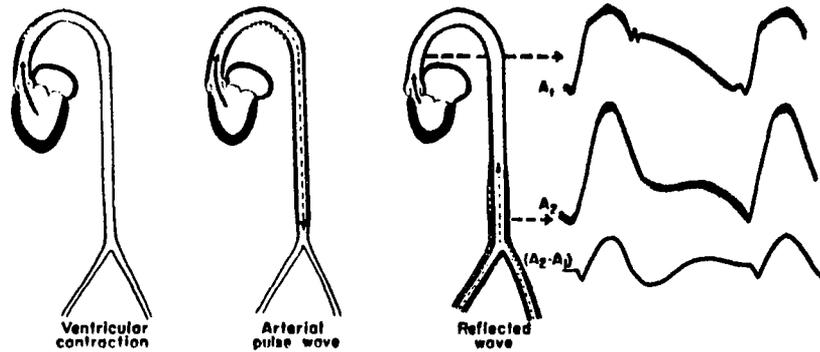
## BLOOD PRESSURE

As a major factor determining the maintenance of circulation in the systemic and pulmonary vascular systems, the blood pressure provides a readily available index of the adequacy of cardiac function. The blood pressure is pulsatile and is composed of a large sustained (dc) component, the mean systolic blood pressure, about which a pulsating (ac) component, the pulse pressure, fluctuates. Major determinants of the form and magnitude of the blood pressure are: a) contractile energy of the heart, b) the quantity of blood in the arterial system, c) the volume flow of blood per beat (stroke volume), d) the elasticity or distensibility of vessel walls, e) the viscosity of the blood, and, f) the peripheral resistance, which is largely determined by the variable caliber of the small vessels. Mean systolic blood pressure can, in fact, be defined as the product of the cardiac output and the peripheral resistance.

Because of the numerous interacting factors, blood pressure is not a simple sustained load. It is characterized by a pressure pulse, the shape of which is the resultant of both the cardiac output flow waveform and the nature of the vascular load impedance. In his analysis of the arterial pulse, Rushmer ( 283 ) observes that at the onset of ventricular ejection, blood flows into the aorta faster than it leaves through the arterioles. Ejected blood accumulates in the first portion of the aorta, thereby increasing the local tension ( Figure 6 ). The increased pressure and wall tension in the root of the aorta force blood into the adjacent segment of aorta which, in turn, is stretched and develops increased tension. In this way, a pulse of pressure moves rapidly down the aorta at a velocity determined by the elasticity of the walls and the pressure of the blood. This pulse wave is transmitted much more rapidly than the velocity of the blood flow. Normal pulse wave velocity in the aorta approaches 3 to 4 meters per second although in the limbs it may be 7 to 14 meters per second. On the other hand the average velocity of blood

## ARTERIAL PRESSURE PULSE

### A. DISTORTION OF THE ARTERIAL PULSE WAVE ALONG THE AORTA



### B. THE VELOCITY OF BLOOD FLOW AND ARTERIAL PULSE IN THE AORTA



*A.* The arterial pressure pulse is a wave of pressure which passes rapidly along the arterial system. Blood suddenly ejected into the ascending aorta at the beginning of systole has insufficient energy to overcome all the inertia of the long columns of blood in the arteries. Therefore, blood tends to pile up and distend the ascending aorta, causing a sudden local increase in pressure. Blood is then forced into the next portion of the aorta, extending the region of distention and initiating a pulse of pressure which travels rapidly along the arteries toward the periphery. These waves of pressure, reflected by peripheral structures, travel back toward the heart and become superimposed on the advancing pulse wave. This produces a higher peak of systolic pressure, a slurring of the incisura and a lower diastolic pressure in the femoral artery. If the peripheral arterial pulse wave is subtracted from the pulse recorded at the arch of the aorta, the resulting wave form ( $A_2 - A_1$ ) suggests a natural frequency of the peripheral arterial system.

*B.* The pulse wave velocity (4 to 5 m. per second) is much faster than the velocity of blood flow (less than 0.5 m. per second). The pulse wave velocity is determined by the elasticity of the arterial walls which, in turn, depends upon their distensibility in relation to the blood pressure.

Figure 6

Source: Rushmer ( 283 )

flow in the systemic circulation is less than 0.5 meters per second. Thus, although the pressure wave may reach the vessels of the foot in 0.2 seconds it requires several heart beats for the blood entering the ascending aorta to reach the foot vessels ( 140 ).

Toward the end of systole, ventricular pressure falls below aortic pressure. The aortic valves close and the resulting back flow of blood produces the characteristic incisural notch in the pressure pulse pattern. As pressures are recorded in arteries progressively further from the heart, the pressure pulse changes in shape and increases in peak to peak magnitude until the smaller arteries are reached. Various causes for these changes are discussed by Rushmer ( 283 ), from different sources, and include the effects of reflected pressure waves rebounding from the periphery, attenuation or damping of various frequency components of the pulse wave, differences in propagation velocity of different frequencies in the pressure-pulse and steady-state oscillation of the arterial system.

The rapid spread of pulse waves and their modification as they pass through the system lead to difficulties in interpretation of blood pressure measurements. Systolic pressure in the peripheral arteries is considerably higher and diastolic pressure lower than at the root of the aorta. Consequently, measurements of blood pressure represent instantaneous values at the site measured only. Furthermore, because of the nature of the waveform, it is necessary to measure both the maximum pressure during systole and the residual pressure during diastole. The difference represents the pulse pressure. Since the waveform is not sinusoidal, the mean systolic pressure is not a simple average, but may be approximated by a value calculated from the diastolic pressure plus one-third of the pulse pressure.

In considering methods for the measurement of blood pressure it is necessary to examine the physical parameters of measurement as well as the physiological. Shirer ( 301 ) has prepared a table outlining some of the relevant parameters ( Table 5 ) which is of particular usefulness in the design and selection of electronic and mechanical transducers.

**TABLE 5**  
**PARAMETERS ASSOCIATED WITH CARDIOVASCULAR PRESSURE**

1) Magnitude	Range	-10 to +300 mm Hg		
	Typical Adult Man	Systolic/diastolic: 130/80 mm Hg Mean: 100 mm Hg		
2) Frequency Spectrum	Mean (dc) Component plus Fundamental (heart rate) plus 6 to 30 harmonics			
	Man	1-3.3 beats/sec	20 cps	66 cps
	Dog	1.5-5 beats/sec	30 cps	100 cps
	Shrew	12-22 beats/sec	72 cps	440 cps
3) Source Impedance	Resistance		Volume Elasticity	
	Man Dog	1 mm Hg-sec/ml, 3 mm Hg-sec/ml,	(Aorta) 0.3-10 mm Hg/ml, [7]. (Arterial system) 0.1-1.0 mm Hg/ml [6].	
4) Noise	Turbulence			
	Acceleration Temperature	Position, $\pm 1g$ ; Ascending aorta, 1-8g; Heart, 0.1-2g Ambient to body, 20° C		
5) Blood	Stray electric currents, electric and magnetic fields			
	Viscosity	3-4 $\times$ water; temperature, composition, and tube diameter dependent		
6) Accessibility	Coagulable			
	Indirect via elastic and viscous tissue Direct via vessel puncture			

Source: Shirer ( 301 )

The table indicates that pressures in the circulation range from about -10 mm Hg above atmospheric pressure at the very lowest to 300 mm Hg at the highest. The negative pressures, of course, are found only momentarily in the large thoracic veins and the heart chambers. The table also indicates the fundamental frequencies and their harmonics. It is generally agreed that high fidelity reproduction of waveform requires a system which will respond linearly to the tenth harmonic of the fundamental frequency ( 136 ). At a maximum heart rate of 240 per minute the pulse frequency is 4 per second and the tenth harmonic 40 cps. Consequently, an ideal system should have a frequency response linear to at least 40 cps, although this is only occasionally achieved.

The table also indicates the source impedance, which has a resistive, an elastic, and a mass component, although only the first two are normally considered. The source impedance is considered in determining the degree to which the measurement variable will be disturbed by the measurement load. In dog and man, the source impedance is negligible compared with that of measurement devices.

The question of noise interference is considered in the table in terms of the effect of turbulence, acceleration, and temperature, along with the effects on the measuring system of stray electric currents, magnetic and electric fields.

Actual measurement of arterial blood pressure can be undertaken using either direct or indirect techniques. Direct techniques involve the cannulation of arterial vessels, which is a procedure both painful and to some extent hazardous. Consequently they cannot be considered for anything other than exceptional use in a manned space laboratory. At the same time, a brief consideration of the principles involved in direct measurement is in order.

## Direct Method

Mercury manometers have been traditionally used for the direct recording of mean systolic blood pressure, via an arterial cannula containing a solution of saline or heparin separating the blood from the mercury. Because of the inertia of the fluid and the resistance to its flow into the manometer, the latter is inadequate for the precise and continuous recording of systolic and diastolic blood pressure. This inadequacy led to the development of devices with a frequency response adequate for the task. These devices initially were mechanical transducers such as that of Hurthle ( 1888 ) (quoted by Green <sup>( 136 )</sup>) who used a mechanical lever system to amplify movements of a membrane. The frequency response of this system, however, was still very low. Improvement came with the development of optical systems in which a weightless light beam was used as the lever, reflecting the movements of a miniature mirror mounted on a rubber or metallic membrane <sup>( 108, 147 )</sup>.

With the development of electronics came the use of devices in which the minute movement of a high frequency membrane is employed to produce changes in resistance, capacitance, or conductance, which can be detected, amplified, and displayed on some form of permanent record.

The resistance principle is used in the Statham gauge <sup>(183 )</sup> in which displacement of a metal bellows produced by increase of pressure is transmitted to a metal slide supported by four sets of strain-sensitive wires wound under tension and connected to form a Wheatstone bridge.

The capacitance principle is employed in a transducer designed such that a metal membrane in contact with the blood flow forms one plate of a condenser, the other being rigid. Changes in the air gap between, cause changes in capacitance <sup>( 195 )</sup>.

An inductance manometer was described initially by Motley et al. , <sup>( 229 )</sup>. In the early form the movable membrane and the secondary coil were placed in the field of a primary coil supplied with high frequency ac current. In later types, the membrane is connected to an iron core

located within the coils. Movement of the iron core produces changes in the magnetic flux <sup>( 123 )</sup>. The latter device can be attached to the end of a cardiac catheter and inserted directly into the heart and great vessels.

All these methods require electronic amplification and display by optical galvanometer, direct writing galvanometer, or oscilloscope and camera, and in each case careful consideration has to be given to the frequency response of the total system. Theory and techniques of analysis of the frequency response are discussed in detail by Shirer <sup>( 301 )</sup>.

Still another system of measurement was developed by Clemedson and his associates in Sweden <sup>( 62 )</sup> using the RCA No. 5734 mechano-electric pressure transducer. The latter is a subminiature triode vacuum tube with a movable anode which is attached to the liquid-containing membrane manometer. Since the anode current is proportional to the distance between the anode and the cathode, any movement of the anode from pressure fluctuation will cause a change in the resulting current and a subsequent variation in voltage across a resistor in the anode circuit, which can be interpreted in terms of pressure.

Direct registration of blood pressure is open to error from such occurrences as impaction of a catheter or cannula against the vessel or heart wall, false readings occasioned by catheter movement in the stream, differences in reading according to whether the catheter is sampling by way of an end or side opening, and problems created by improper frequency response or inadequate damping, but there is little doubt that direct methods must be inherently superior to indirect, and in fact the direct mercury manometer technique can be regarded as a standard. However, because of difficulty in execution, discomfort, and potential hazard to the patient, the use of direct methods of blood pressure measurement would not seem justifiable in a manned space laboratory.

## Indirect Methods

Indirect methods avoid the problems of cannulation and provide a measure of blood pressure by the use of devices designed to match the pressure within the artery or to reproduce the pulsatile distension of the artery. Systolic pressure is recognized as being that pressure just less than that required to occlude flow in an artery. Diastolic pressure is the maximum amplitude of the residual pressure when flow is re-established.

### Manual Sphygmomanometry

The manually operated sphygmomanometer is the most common, simplest, and, when properly used, probably the most reliable method available for indirect measurement of blood pressure.

It is not necessary to detail the technique, which depends on occlusion of an artery by way of pressure applied through a suitable inflatable cuff, visual estimation on a manometer or aneroid scale of the pressure at which the flow is re-instituted, and further estimation of the pressure at which flow is established.

Recognition of these two pressure points depends on perception by stethoscope over the brachial artery of the sounds described by Korotkow in 1905, which are alleged to be caused by turbulent flow occurring in the vessel partially compressed by gradually reducing pressure in the cuff. Four phases of these sounds are described (140):

Phase 1. Sudden appearance of clear, but often faint, tapping sound growing louder during the succeeding 10 mm Hg fall in pressure.

Phase 2. The sound takes on a murmurish quality during the next 15 mm Hg fall in pressure.

Phase 3. Sound changes little in quality but becomes clearer and louder during the next 15 mm Hg fall in pressure.

Phase 4. Muffled quality lasting throughout the next 5 to 6 mm Hg fall. Thereafter the sound disappears.

Systolic pressure is measured at the onset of phase 1. According to the American Heart Association (40) diastolic pressure is measured at

the cessation of sounds. This recommendation has been questioned, particularly by Roberts and his colleagues ( 274 ) and by Burton ( 51 ), who in comparison studies between sphygmomanometry and direct manometry produced strong evidence to indicate that diastolic pressure is better indicated by the point at which muffling occurs.

Several sources of error exist in measuring blood pressure by sphygmomanometer, in addition to subjective errors in interpretation of the sound. One relates to the relative size of the cuff and the arm. The standard cuff is 13 cm wide. If the cuff is small relative to the arm the pressure around the artery when the cuff is inflated may be considerably less than that recorded by the manometer ( 326 ). Similarly, if the cuff is too loosely applied it tends to become more cylindrical when inflated, with a reduced area of application, thus producing the same effect ( 282 ). Reading errors can also occur because of too rapid deflation. Another source of error is known as the auscultatory gap ( 35, 263 ) which describes the phenomenon in which the auscultatory sounds in some cases disappear over a fairly large range between systolic and diastolic pressures, although the radial pulse is preserved. The occurrence of the gap is related to a slow rate of inflation of the cuff. It may be eliminated in some subjects by inflating the cuff with the arm elevated. The cuff should be inflated as rapidly as is feasible to a point about 30 mm Hg over the point at which the radial pulse disappears and then deflated at the rate of 2 to 3 mm Hg per heart beat ( 40 ).

Despite the potential errors, the method when properly used is very reliable and strongly supported by tradition. Several studies have been undertaken comparing blood pressure values obtained by a sphygmomanometer with those obtained by direct means ( 153, 263, 274 ). Differences would appear to be of the order of  $\pm 8$  mm Hg. Both the apparatus and the technique of sphygmomanometry are simple, and the method deserves strong consideration for use in a manned space laboratory.

### Automatic Sphygmomanometry

While the manual system is convenient for discrete and discontinuous readings, it is unsuitable for monitoring purposes, and during limb movements. Several approaches have been made towards modifying the technique for automatic continuous registration. These may be considered in three major groups, namely: a) those in which Korotkow sound from an artery below the cuff are recorded visually in conjunction with cuff pressure, b) those in which pressure pulsations from the artery are recorded graphically from a subsidiary pressure bag under the cuff, along with cuff pressure, and, c) those in which cuff pressure is controlled at systolic level by a feedback mechanism sensed from an artery distal to the cuff. The last named method, as exemplified by the work of Doupe et al., ( 79 ) and Green ( 137 ), is probably the least satisfactory since not only does it require constant pressure on the limb over a prolonged period, but it is not suitable for the measurement of diastolic pressure.

Recording of Korotkow sounds along with pressure began with Gilson et al., ( 129 ). Other developments on the technique have been made by Rose and his colleagues ( 281 ), and a step forward was taken when Currens and his group ( 72 ) from the Massachusetts General Hospital obtained the pressure and arterial sounds on the same calibrated trace. Continued development culminated in the systems produced by the Wright Air Development Division ( 164 ), by the School of Aviation Medicine ( 277, 307, 329 ) and by AiResearch, for use in the Mercury and Gemini project.

All the devices work on the same principle, but differ in sophistication, pick-up, and filtering. The WADD device (Model 16 ) is the most sophisticated, and correspondingly the most complicated. It utilizes a computer-controlled programme to inflate the cuff, search for a diastolic pulse sound, confirm the latter by a coincident pressure pulse, reconfirm, and go on through a series of steps to identify and confirm a systolic pulse. Auditory ambient noise is minimized by the use of a contact type microphone. The equipment is fairly large and heavy ( 11" x 11" x 11", 35 lbs. )

and, although elegant in concept and use, would not appear to be altogether suitable in its present form for conditions of manned space flight.

The system developed at SAM employs a cuff inflated electromechanically by a bypass type gas pressure regulator with a pressure compensation system to allow for changes in cuff pressure with muscle movement. Readings can be made every minute as follows: inflation (0-225 mm Hg), 3 sec; leak down to dump pressure level, 25 sec; dump (20 - 0 mm Hg), 2 sec; interval to next inflation, 30 sec. The slower the leak down rate the more accurate is the reading. At the same time the longer the cuff pressure is held, both for the duration of a given reading, and in accumulated duration, the more likely is the pressure affected by the measuring device. Thus, an inevitable compromise arises between duration of leak down and duration between readings.

A contact piezoelectric microphone is firmly "potted" in the cuff along with a miniature preamplifier, and the cuff is so placed that the microphone is held over the antecubital fossa, or the medial aspect of the upper arm, preferably the latter to permit easier movement. Electronic filtering of the signal from the Korotkow sounds is so designed as to permit selection of several narrow wave bands for amplification and display. The bands that have been used are those centered on 40, 90, and 150 cps. With suitable selection of a band or bands it has been found that environmental noise rarely interferes with the signal even in the presence of F-100F engine noise at 125 db. Cuff pressure is displayed as a separate simultaneous trace.

In a test with the system in F-100F aircraft, 874 recordings were made during 19 flights with 85% successful records in conditions that include  $\pm 4G$  and short periods of weightlessness ( 329 ). With continued attention to the system such as would be possible in an orbiting laboratory, the expectation of success would probably be higher.

Other testing on a T-33 aircraft has been carried out at Ames Research Center using a different microphone and a filter with a bandpass between 150 and 200 cps ( 307 ). The accuracy of the system was stated to be within  $\pm 4$  mm Hg, assuming a steady heart rate.

Roman and his colleagues ( 277 ) undertook a comparison, under flight conditions in the X-15 aircraft, between the SAM system and a direct arterial method utilizing a Statham strain-gauge transducer. Although only one subject was used, the indirect system was found to be highly accurate and reliable. The values tended to read low, with an average systolic error of -6.7 mm Hg and a diastolic error of -3.3 mm Hg.

The AiResearch system works on the same principle. A special directional contact microphone is held in the pocket of a cuff positioned over the brachial artery. The cuff is automatically cycled with a rapid rise time and a bleed off over a period of about 20 seconds, and a further 30 second delay before repeating. Readings can be made every minute. The microphone signal is passed through a very narrow bandpass filter centered at 35 cps. Body motions and ambient noise affect the signal very little. A major advantage in display over the SAM system is that the sound signal is presented on the same trace as the cuff pressure, which renders reading of the pressure simpler and more accurate. The accuracy of the system is stated to be  $\pm 6$  mm Hg. Reading is occasionally complicated by difficulty in identifying the first systolic pulse. Satisfactory performance has been found under conditions of environmental stress, including 50 G impact shock, 30 G vibration to 2000 cps, sustained acceleration of 10 G, and a temperature range of 0 - 160° F. A prototype system has been used widely under conditions of rest and exercise by Luft at the Lovelace Foundation and has been found highly satisfactory. The system actually used in the Gemini mission had a manually operated cuff, activated by the astronaut as desired, with a miniature signal conditioner weighing 1.6 ounces, from which signals were telemetered to ground-recording oscillographs. Performance was highly satisfactory.

It is apparent that there is little if anything to chose between the SAM and the AiResearch systems. In each case the weight, volume, and power requirements are compatible with the facilities of a manned space laboratory. The signals of each are suitable for telemetry. The SAM system has been operationally tested under severe flight conditions and the AiResearch

system has been operationally tested, at least in part, under orbital conditions, and widely on the ground. The SAM system has an advantage of selective filtering, but presents the cuff signal separate from the arterial signal. The AiResearch system has a single, although effective, bandwidth, but presents a combined cuff and arterial signal.

As mentioned earlier, another approach to automatic sphygmomanometry lies in sensing the pressure pulse by way of a bag underneath the occluding cuff. This approach has been used by Zuidema and his associates ( 352 ) at WADD, and in another form by Richardson et al., ( 271 ) in Oxford. In Zuidema's system, a fluid filled plastic balloon situated underneath the cuff and overlying the brachial artery transmits the pulse waves by way of a polyethylene catheter to a Statham pressure transducer from which they are recorded simultaneously with the automatically controlled cuff pressure. Control of cuff pressure is similar to that described for the microphone system. With 90 determinations on 10 seated subjects, a correlation of 0.97 was found with auscultatory sphygmomanometry.

In Richardson's system, the underlying bag and the cuff are both inflated simultaneously with air. Oscillations from the underlying bag, synchronous with the pulse, are amplified pneumatically and recorded along with cuff pressure during one minute in every five. Comparison with an intra-arterial method showed that in 87% of simultaneous measures the cuff value differed from the intra-arterial value by 10% or less, and in 99.9% by less than 20%.

Not much work, however, has been done with "bag" methods and there seems to be little reason at this time to consider they have any advantage over microphone pickup systems which have been more fully investigated.

#### Methods Using Photoconduction

The volume of blood in a vascular network fluctuates cyclically with each pressure pulse. The change at the periphery is slight but it may be detected by observing changes in the transmittance of a beam of light passing through the tissue. Using a sensitive crystal photocell, a low

intensity light source, and an amplifier, fluctuations can be picked up from any mass of tissue which has a vascular supply and through which the light can be transmitted. Following occlusion of the blood supply to the tissue by applied pressure, and subsequent reduction of pressure, re-instatement of the pulse can be observed at a pressure corresponding to systolic pressure, while maximum amplitude of the pulse wave is noted at diastolic pressure.

Wood and his colleagues ( 346 ) at the University of Rochester, estimated the arterial blood pressure by measurement of the externally applied pressure required to obliterate the ear opacity pulse. For this purpose they used a modified oximeter earpiece with a translucent pressure capsule along with masking which permitted light access through two irises 8 mm in diameter. The pressure capsule was inflated by a bulb connected to a manometer. Blood pressure was also simultaneously measured by intra-arterial and auscultatory methods in the brachial artery. In 20 subjects a closer correlation in systolic pressure was found between the ear pulse and the intra-arterial method than between the auscultatory and intra-arterial, while the values for the diastolic correlated without significant difference in all methods.

While the use of this method is not specifically advocated for manned space use, it should be borne in mind if the ear oximeter system is considered for use in determining cardiac output (see Cardiac Output).

Other applications of the principle have been used for measurement of blood pressure in the finger or toe ( 275, 337 ). The greatest protagonists of this technique, however, are probably Gowen and Bolie ( 36, 133 ).

In their technique, the finger is placed in a device which incorporates an inflatable finger cuff around the base of the finger and a photoelectric sensor at the nail bed. On activation, and controlled by a complex electronic system, cuff pressure is permitted to rise until the finger pulse disappears. A diastolic detecting circuit observes the point where the pulse amplitude begins to decrease, and displays the information on a

digital meter from the output voltage of a pneumatic pressure transducer at the cuff. Simultaneously the information is automatically printed out. When the finger pulse disappears the systolic pressure is displayed on another meter and printed out. Pressure is then automatically released, and a few seconds later the meters are reset. Up to ten pressure measurements can be made per minute. As an alternative to the digital read-out, the information can be displayed as a trace of arterial pulsation along with a calibrated trace of cuff pressure.

Using a small number of subjects, Gowen found a fairly good agreement between systolic pressures obtained by the auscultatory method over the brachial artery, and the finger method with the cuff around the proximal phalanx. A less good agreement was observed with diastolic measures. Statistical analysis was not attempted.

The system has been employed under exercise, but digital read-out or interpretation of the record, particularly for diastolic pressure, is handicapped by noise which occurs with any appreciable hand motion or finger tremor, while, in addition, changes in peripheral motor tone are readily reflected.

While the system has potential for space use, it would appear to be most suitable for monitoring under quiet steady conditions such as sleep or anesthesia. The fact that readings are grossly disturbed by movement, and that immobilization of the hand is required during measurement, renders it less valuable for measurement under active conditions. The equipment meantime is bulky, although it could no doubt be miniaturized.

### Pulse Sensing Devices

Direct external sensing of a peripheral pulse without cuffs or cannulae is an obvious challenge. Analytically and experimentally, cyclical arterial distension varies in a near-linear manner with fluctuating systolic and diastolic pressure. There is a straight line relationship over a large range of pressures although the functional relationships vary from patient to patient and with age. In sensing pressure externally, however, problems

arise because of the necessity for transmission of the waveform through the vessel wall, overlying tissue, and skin. Changes occur dependent upon the geometry and properties of the intervening tissue. Factors involved include elasticity, viscosity, mass, friction, degree of artery occlusion, vasoconstriction or dilation, and muscle movement ( 272 ).

Several early attempts at pressure sensing using spring mechanical transducers were unsatisfactory, largely because of the mass and inertia of the mechanical systems. Adams, Corell, and Wolfeboro ( 1 ), however, on the basis of work done by Corell on capacitance transducers, developed a system whereby deformation of skin surface overlying an artery was used as an index of the diametric change in the artery with the pressure pulse. The system recorded reproducible pressure pulses which could be calibrated in terms of blood pressure and gave, under best conditions, an accuracy within 3% to 8% of that obtained by a direct intra-arterial method. The system, however, was readily open to error resulting from limb movement, transducer motion, and transducer location, while calibration was readily lost. In addition, physiological influences on skin tension, tissue tension, and muscle tone were found to exert a profound effect on the reading. Thus, although certain drugs would reduce arterial pressure the accompanying effect on tissue would be such that the sensor would read a relative increase in arterial distension. Consequently, while the system has advantages, these are largely nullified by the disadvantages.

Another form of capacitance device is marketed by Gulston Industries (The Infracron pickup, Model B ) and described by Gaffey ( 117 ). It incorporates in the system a manually operated finger cuff on line with a manometer. The cuff is used both for holding the transducer in place and for calibration purposes. The system has been used at several hospitals and research institutes for blood pressure recording, but, at least on theoretical grounds, it would seem to suffer from the above noted disadvantages.

To overcome these disadvantages, Pressman and Newgard ( 258, 259 ) tried a different approach. Instead of sensing the skin deformation over an artery they applied a controlled pressure over the area sufficient to flatten the skin and tissues under the transducer and remove tissue tension effects, and at the same time, in the center of the flattened area directly overlying the vessel, they independently applied pressure sufficient to flatten the vessel slightly. They then sensed the force required to maintain the vessel slightly flattened in the face of the internal pressure pulse. In their initial device, the mechanics of which they justified by an elegant mathematical model ( 258 ), they used a strain gauge transducer with pneumatic pressure loading. The transducer could be mounted over, for example, the radial or temporal artery. Pressure was applied from an air pressure chamber in the transducer via a rubber diaphragm to the skin. Sideplates, integral with the housing, lay on each side of the artery, and the center plate, or rider, which was in communication with the strain gauges, lay directly over and partially compressed the artery ( Figure 7 ). A satisfactory method of calibration was developed, using an artery simulator which could be pressurized in a controlled manner. The initial devices were sensitive to temperature, positioning of the transducer, motion, and size of the rider as compared to the artery, but changes in design and care in application produced results in man comparable with those from a sphygmomanometer, and at the same time allowed continuous beat-to-beat blood pressure evaluation.

Continued development, particularly with respect to the operation of a temporal sensor, led to the use of a much smaller rider which in turn utilized a smaller fraction of the energy derived from the blood pressure and dictated the requirement for a transducer other than the strain gauges previously used. Consequently, a new device was developed ( 259 ) which used as a sensor a miniature differential transformer. This transducer in turn suffered from a high acceleration sensitivity, amounting initially to as much as 50 mm Hg per g. Design changes and mechanical compensation reduced this to a measured value of less than 2 mm Hg per g. This new model is not temperature sensitive, and in addition methods are being devised to permit accurate semi-automatic positioning of the

transducer in the optimum location over an artery.

This system for external sensing of blood pressure is still under development and cannot yet be considered for use in space conditions. It shows great potential, however, as a method for continuous, non-cuff, non-cannula, beat-to-beat, external sensing of arterial blood pressure via the temporal artery.

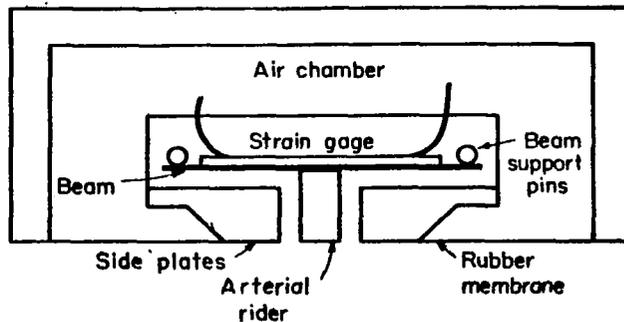


Figure 7

Source: Pressman and Newgard (259)

### Ophthalmodynamometry

In a very comprehensive review of the subject of ophthalmodynamometry, Koch (175) observes that the eye may be converted into a natural sphygmomanometer. With application of external pressure, a pulsation in the retinal vessels is induced. Initially venous pulsation is observed. As intraocular tension arises to equal diastolic pressure, collapse of the retinal arteries occurs in diastole, and pulsation of the arteries becomes visible. Further increase of intraocular pressure to systolic level causes total collapse of the arteries and disappearance of pulsations. Pressures applied to the living human eye can be registered by a standardized tension spring instrument. Numerous modifications of the instrument have since been developed. With this, or similar,

apparatus, pressure is applied horizontally to the sclera while the retina is observed by ophthalmoscope. The applied pressure at diastolic and systolic levels is read from a scale on the instrument.

Another modification of the principle was developed by Thorner ( 327 ), who devised a transducer called the ophthalmic Pulsensor, by which air pressure is applied to the eye and the resulting pulsations transduced and recorded on a trace which is interpreted in a manner similar to a digital pulse trace. Use of the instrument in over 700 cases is reported by Kimura and Kaslow ( 160 ).

A third modification relies on the plethysmographic goggles developed by Weeks and his associates ( 336 ), and depends on the subjective response of the subject viewing a target. It has been suggested by Lewis and Duane ( 189 ) that the occurrence of greyout is associated with an increase in intraocular tension to diastolic level, while the occurrence of blackout is associated with increase to systolic level. Consequently, by increasing the pressure over one eye to greyout level and then to blackout level, an estimation of diastolic and systolic pressures can be made. These assumptions have not been validated.

These three methods all suffer from inadequacies. The existence of a natural intraocular tension of some 20 mm Hg confuses the readings, while there is some possibility that the application of external pressure per se may affect the arterial pressure locally or centrally. In addition, application of pressure by the spring tension instrument method and subsequent reading of the record is open to considerable subjective error on the part of the investigator, while differences would also appear to occur by reason of different designs of the instrument. In any event, a wide range of results has been observed with the spring technique, up to as much as 100%. Koch ( 175 ) states that the average retinal artery pressure so obtained is 30 to 45 mm Hg diastolic, and 65 to 75 systolic.

The Thorner technique suffers from the same problems in utilizing the eye as a sphygmomanometer, but is probably more reliable in its reproducibility. Kimura and Kaslow ( 169 ) state that comparisons of

Pulsensor data with readings derived from a catheter in the common carotid artery show agreements within 10%. It must be noted, however, that both the spring tension and the Pulsensor methods are preferably conducted with local anesthesia of the eye, a fact which renders them very unsuitable for space use.

The plethysmographic goggle technique is as yet not validated. It seems doubtful, however, if it would provide useful general information on blood pressure more simply than other techniques, although it might well be used to obtain information on retinal circulation.

### Electrical Impedance Plethysmography

Plethysmography of various types has been extensively investigated from the point of view of providing measurements of blood flow. In point of fact, many of the methods previously described for determination of blood pressure employ the principles of venous occlusion plethysmography, in that external pressure is applied to a body segment and initially occludes venous flow before going on to occlude arterial flow.

The technique of segmental limb electrical impedance plethysmography, the principles of which are described in the section on Cardiac Output, also shows potential in this area. Allison <sup>(2)</sup> demonstrated that if pressure is applied to a limb by way of a sphygmomanometer, changes in the electrical impedance waveform downstream could be read in terms of blood pressure. From some points of view the technique shows more reliability in measuring diastolic pressure than do the more common oscillometry methods. Ideally, diastolic pressure is measured at the level of appearance of the dicrotic notch from the pulse waveform. In the standard oscillometry techniques, where the pulse is sensed from a transducer under the sphygmomanometer cuff, the pressure actually sensed is a function of both the intra-arterial pressure and the externally applied transmural pressure. Because of the associated pressure-volume relationships under the cuff, and the accompanying changes in segmental compliance, the disappearance of the dicrotic notch is unreliable under these circumstances as an index of diastolic pressure, and the maximum amplitude of the pulse is used

instead. With the impedance system, however, sensing takes place downstream of the cuff where these altered relationships do not apply, and the dicrotic notch can be used as a reproducible index of diastolic level.

Very little has been done to develop impedance techniques for the measurement of blood pressure, but if impedance instrumentation is available on the spacecraft for other purposes, as is recommended, the potential of using this instrumentation for blood pressure measures would be a useful dividend. It would be particularly valuable to develop independent calibration measures so that the waveform could be used for determining blood pressure without the need for a sphygmomanometer cuff.

### Venous Pressure

Measures of venous pressure may assume considerable significance in space operations where cardiac decompensation arising from weightlessness and/or confinement may be reflected in venous pooling. Although information is desirable on both peripheral and intrathoracic venous pressures it is considered that measures of the latter, which require cannulization from the periphery to the great veins, are inadvisable and unjustified under the circumstances. Useful qualitative information, however, can be obtained by applying a transducer (microphone, capacitance) over the jugular vein and obtaining a trace of the venous pulse. It is probable that methods could be developed for calibrating this pulse in terms of pressure.

Peripheral pressure can be evaluated by means of a simple manometer attached by a three-way stopcock to a syringe and needle. Saline is ejected from the syringe into the manometer to a level above expected venous level, and then, by use of the stopcock allowed to enter a peripheral vein. Final saline level in the manometer represents venous pressure which, in turn, should be related to the phlebostatic level. In an alternative method, saline from a capillary tube with a pre-established meniscus is allowed to run horizontally into a vein by way of a needle on the capillary tube. The position of the meniscus moves

outward and is returned to its original position by air pressure applied via a rubber tube and pressure bulb attached to the other end. A manometer in series with the bulb provides a reading of the pressure level ( 50 ). A further modification of this technique by Sodeman ( 310 ) obviates the requirement for a manometer by the use of a system in which the restoring pressure is applied by controlled increase of tension on the bulb through rotating a knob on a calibrated dial. This last system, which seems to be that of choice, is probably open to further development in miniaturization.

### Recommendations

In making recommendations on techniques for determination of blood pressure in manned space laboratories it is necessary to consider the requirements for these measures. As an index of the adequacy of the cardiovascular system, blood pressure measures can be used in three ways: continuous monitoring, routine discrete determination, and short duration observation. In the early stages of space exploration such as is exemplified by the Mercury, and Gemini missions, continuous or nearly continuous monitoring of vital functions, of which blood pressure is one, has been the practice wherever possible. As knowledge of man's immediate response to the space environment increases, as missions become longer and more sophisticated, and as environmental control systems more nearly perfect, the requirement for continuous monitoring of blood pressure, in particular, disappears. In the space laboratory situation, however, there will still be a requirement for both discrete measurements to identify trends and for short duration observations during physiological experiments, and perhaps during extra-vehicular activity.

For discrete measures, there seems no reason to doubt that the manually operated aneroid sphygmomanometer and cuff, when properly used, is the simplest, most reliable, and most thoroughly investigated of all techniques, and can provide values of acceptable accuracy.

For short duration observation, a continuous readout, preferably on a beat-to-beat basis is desirable. Beat-to-beat methods include techniques involving photoconduction ( 36, 133, 346 ) , pulse sensing and perhaps impedance plethysmography, but none of these methods as yet appear to be developed to a stage of superiority, although obviously they deserve continued application and might well be used in an experimental manner, particularly if the instrumentation is already available for other purposes.

Consequently, for short duration observation the methods of choice would appear to lie with devices sensing a pulse from beneath an automatically inflated sphygmomanometer cuff. As previously noted there is little if anything to chose between the SAM development and the AiResearch development. Each would appear to perform an adequate function and each has advantages not possessed by the other.

While the automatic sphygmomanometer appears to be the method of choice at this time it is obviously not an ideal piece of apparatus. It is bulky, very indirect, mechanically complex, sometimes difficult in systolic reading, and provides only partially continuous observations. It seems probable that greater potential lies with direct pulse sensing devices not requiring a cuff. Continued improvement and development of these methods, particularly with respect to temporal artery sensing, would be desirable.

## CARDIAC KINETICS

Traditionally it has been the practice for the clinician to place a hand on the thorax over the point or area of maximum cardiac impulse and thereby obtain by way of a complex indefinable judgmental process an indication of cardiac function. To the trained and experienced clinician this is a reliable and informative technique. Obviously, however, it is subjective, non-quantifiable, and impermanent.

Towards the end of the 19th century, Gordon <sup>( 131 )</sup>, in Edinburgh, while engaged in careful body weight measurements with a spring balance, observed rhythmic fluctuations in the balance movement which he showed were correlated with the cardiac cycle. From that point on, evolution of techniques for the representation of cardiac kinetics was slow. With the appearance and subsequent development of electronic techniques of transduction and recording, interest was re-awakened, but the development of these same techniques led in turn to great confusion in nomenclature and interpretation of the records obtained.

Rosa <sup>( 279 )</sup> points out that the pulsation which is experienced over the chest and elsewhere is derived from contraction of the heart, and can be expressed as the resultant of several vectors. At the same time the heart cannot be vectorally separated from the totality of the vibrating body, which includes the blood mass and the vascular tree. The major contribution to the energy input is derived from the left ventricle which provides most of the energy of cardiac contraction (Agress et al., <sup>( 3 )</sup>).

One representation of the resulting forces is found in the ballistocardiogram (BCG), modified from Gordon's spring balance, which reflects some aspects of the relative motion between the heart and the body that results from heart action. As a result of heart activity, blood is displaced from the ventricles, the position of the heart in the thorax changes, and a pressure wave develops along the long axis of the vessels. Ballistocardiography examines the end result, a shift in the body's center of gravity,

which can be registered as a displacement, velocity, or acceleration, measurable in three mutually perpendicular axes. From its original inception, BCG technique has undergone considerable evolution, culminating in the high frequency BCG of Starr et al., ( 313 ) which tended to produce distortion of the record at the natural body frequency of 5 cps, and the still later ultra-low frequency systems of Klensch and others.

Ballistocardiography, however, has inherent disadvantages. Chief among these are the requirements for bulky and costly equipment, distortions of waveform attributable to different body masses, distortions induced by the masses of the limbs, changes in impedance inherent in the coupling between the body and the table or suspension, and perhaps inconsistent abnormalities occurring in the records of subjects over age 40 ( 3 ). Theoretically, some of these disadvantages can be overcome by obtaining records during the weightless state. To this end 6-degree of freedom free-floating ballistocardiography has been suggested by Lockheed researchers as a possible technique for use in space missions ( 199 ). The Lockheed group presumably bases its suggestion on the work of Tannenbaum, et al., ( 321 ) in spatial vector ballistocardiography, but has not so far carried out any experiments in this field. They envisage a light platform, of the nature of a tubular frame, on which the subject is mounted free-floating. Six accelerometers record in three linear and three rotational vectors. The record is then integrated by computer into a single measure recording a spatial vector ballistocardiogram. A somewhat similar technique has been utilized by Hixson and Beischer ( 157 ), of the U. S. Navy School of Aviation Medicine, who have undertaken measurements on subjects flying a Keplerian trajectory in a KC-135 aircraft. Using a custom-moulded fiberglass couch, and three orthogonally mounted linear accelerometers along with one angular accelerometer, they obtained data on the triaxial ballistocardiograph in the free-floating state. Signals were conditioned on board and telemetered to an airborne receiving station. At the same time

they obtained triaxial electrocardiographic data for correlation of the electrical and mechanical events of the cardiac cycle. The resulting data were voluminous and difficult to interpret. Acceleration patterns were displayed in loop form and in a three-dimensional model to assist in visual analysis, and, in addition, a computer analysis of the data was undertaken. It is interesting to observe that the longitudinal ECG component in the flight data conformed closely to that found in terrestrial ultra-low frequency systems with close body-suspension coupling. The absence of comparative data, in other vectors unperturbed by gravitation, renders interpretation difficult, and much more baseline data is required.

It is apparent, however, that the system shows great potential, despite the complexity of the procedures required in continuing investigation in a nulled-gravitational environment. It seems reasonable to assume that in conditions of actual space flight the restraint and instrumental complexity will be to some extent reduced. The main considerations at this time appear to be refinement of instrumentation, collection of baseline data, and development of a simplified form of data analysis.

The disadvantages inherent in ballistocardiography in terrestrial gravitational conditions have led to closer consideration of techniques of recording and analysis of precordial vibrations. Since the characteristics of these vibrations reflect heart motion, analysis of the waveforms can be used to assess the events of the cardiac cycle, and the rate of contraction and relaxation, as well as correlative data pertaining to blood flow and cardiac output.

In the process of pumping blood, work is performed and energy developed. Some of this energy can be appreciated over the precordium as vibrations in a range from below 2 cps to above 1000 cps. Figure 8 modified by Agrest from Butterworth, indicates that the spectrum has a wide range of energy distribution, being markedly more intense at the lower frequencies. The high-speed components (murmurs) are produced by acceleration and impaction of high-speed jets of blood or

# HEART VIBRATIONS FREQUENCY-ENERGY DISTRIBUTION

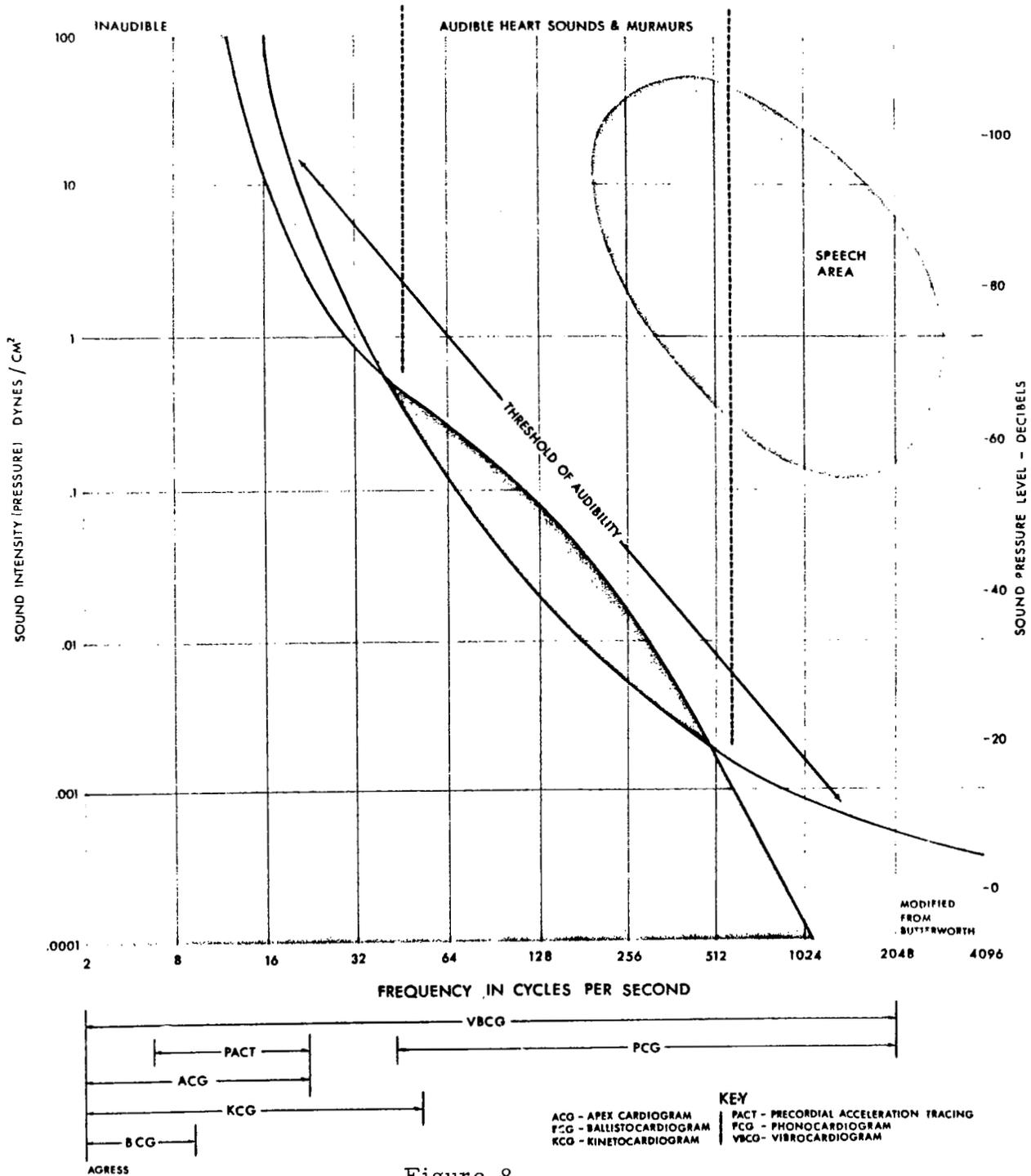


Figure 8

Source: Agress and Fields, ( 2 )

from turbulence around small masses of tissue or valves. The lowest frequencies, those approaching the fundamental frequency of heart rate (about 1 cps), are generated by the motion of the heart in conjunction with, and coupled to, the major volume of blood moved ( 2 ).

As can be observed from the figure, the measurable range of audible vibrations ( 40 to 500 cps), occupies about 1% of the total. Since the original work of Marey ( 209 ), who developed a system of recording chest motion from a bellows tambour over the precordium, numerous techniques have been developed to investigate the remainder of the vibrational field. In general, however, five distinct, though related techniques have evolved, namely, the apexcardiogram, the kinetocardiogram, the precordial acceleration tracing, the phoncardiogram, and the vibrocardiogram. The frequency ranges explored by these techniques are indicated in Figure 8.

The apexcardiogram, recording displacement at the cardiac apex, has received much attention since its inception by Marey, and has been found of particular value in the study of hypertrophy, valvular lesions, constructive pericarditis, bundle branch block, and cardiac aneurysm.

The kinetocardiogram was described by Eddleman, et al., ( 89 ). It utilizes a technique whereby a bellows pickup is suspended from a fixed point above the chest wall. The air coupling ensures reproducibility, avoids phase distortion occasioned by differential motion between the tissue and transducer, and records pure displacement tracings, as well as picking up diffuse precordial motions that might be poorly registered by a transducer directly on the chest wall. Kinetocardiography has been used in the investigation of valvular heart disease and ischemic heart disease, with some success, but its limitations for use in space vehicles seem to be prohibitive.

The precordial acceleration tracing (PACT) was developed by Rosa, et al., of the Chicago Medical School, although some of the original observations were made by Landes ( 184 ). The technique employs an electromagnetic accelerometer operating in a defined frequency band ( 2 - 30 cps ) and uses standardized procedures for obtaining reproducible

data. Rosa and his colleagues have undertaken considerable work with this system and have described criteria for the normal PACT ( 280 ), and its use in clinical interpretation ( 279 ).

The output voltage tends to vary with the tissue, and presumably the impedance of the tissue, over which the vibrations are being registered. As a result, with the electromagnetic microphone type transducer used by Rosa, records registered over soft tissues may in fact represent reflections of velocity and not acceleration. Notwithstanding allowances for resonance vibrations, however, and attenuation by intermediate structures, Rosa has shown that the PACT offers a reproducible standard by comparative studies. Time sequence, frequency pattern, and relative amplitude of the consecutive oscillations reveal a pattern equivalent to the second derivative of the pressure curve obtained from the pulmonary artery and the aorta, and the time tracings relate to mechanical events in the cardiac cycle.

Noting the phase relationships in tracings representing displacement, which is proportional to the ventricular pressure pulse, velocity of vibration, and acceleration, Rosa maintains that the acceleration tracing is richer in useful detail than displacement tracings, as well as being less subject to distortion from respiratory movement. During ventricular isometric tension, contractile forces without motion are paramount, and thereafter, there is a phase difference between the velocity of the resulting motion and the acceleration component of the force during it. The acceleration tracing reflects forces in the antero-posterior vector rather than motions, and shows details absent in displacement tracings during isometric contraction.

The transducer used by Rosa, however, which is manufactured by the Decker Corporation, is cumbersome, with a weight of 100 Gm and a diameter of 40 mm, and it is doubtful if the technique would have direct application to space use. In addition, its output is not quantifiable in absolute terms, and, as has been noted, there can be some doubt as to whether the transducer reflects velocity or acceleration.

The use of a strain gauge accelerometer has much to commend it. Proper, of the Lovelace Foundation ( 26 ), is using a light-weight,

miniature ( 1 cm diameter) Statham strain gauge accelerometer which records in the range of 0.1 to 20 cps. In that range its response is linear, reflecting only acceleration, and is quantifiable to  $\pm 5g$ . A considerable body of data has been accumulated with this technique, defining normal precordial acceleration patterns in selected subjects of varying ages. The simplicity of the sensor and signal conditioners, and the reproducibility of the tracings renders the technique of particular advantage in space operations. Further application of this technique will be considered later.

Much work has been done with the phonocardiogram since the initial description of the technique of recording heart sounds was made by Einthoven and Geluk in 1897. Development of suitable electronic pickups, amplifiers, and filters, has led to more and more refinement in defining, through various frequency bands from about 40 - 1000 cps, various heart sounds, murmurs, snaps, and friction rubs, and in utilizing these sounds to time events in the cardiac cycle.

Numerous authors, including Landes ( 184 ), have observed relationships between the phonocardiogram, particularly in the low frequencies, and other recordings of precordial vibration, notably the PACT ( 291 ). The resemblance to the PACT is particularly obvious, since in the frequency range below 20 cps the microphones used in phonocardiography do not have a linear response, and in fact probably reflect distorted acceleration complexes ( 279 ). As will be noted later, the phonocardiogram is, in fact, a filtered apexcardiogram.

While phonocardiographic techniques could be utilized in space operations and render useful information, it is doubtful if the information so obtained would warrant the additional complexity, particularly when a large portion of that information can be obtained by the stethoscope and other methods to be described.

As will be observed from Figure 8, the techniques of vibrocardiography explore the whole frequency range of precordial vibrations. Although the term was originally coined by Kountz, Gilson, and Smith in 1940 ( 176 ), the most comprehensive work in this field has been done by Agress and his colleagues at the Institute of Medical Research,

Cedars of Lebanon Hospital, Los Angeles. In addition, clinical application of the techniques has been effectively undertaken by Proper at the Lovelace Foundation. Essentially, the vibrocardiogram (VbCG) trace is a time function of the total vibrational energy appreciated over the precordium in frequencies ranging from less than 1 cps to over 2000 cps. Initially an Altec capacitance microphone was used as the sensor, but more recently miniature microphones with signal conditioning transistorized for minimal size, manufactured by Ling Temco Vought, have been utilized with even greater success. This equipment has a linear response in the frequency range 1.6 cps to 3000 cps ( $\pm 3$  db) and a dynamic range of 90 db. Still further refinements of the equipment are currently under study.

Figure 9 illustrates the form and standardized nomenclature of the VbCG trace, although it must be noted that the form, although not the timing, tends to change with the position of the transducer on the chest, and the position and physical characteristics of the subject. Figure 10 illustrates the time sequence of the VbCG in relation to the ECG, the phonocardiogram, and pressure events in the cardiac cycle.

According to Agress, measurement of the phases of isometric contraction, ejection, systole, and diastole can be obtained from the precordial VbCG with an accuracy as good as that realized with direct cardiac catheterization. In addition, comparison of these phase intervals in stressed and unstressed subjects has shown significant changes which serve to differentiate the normal from the cardiac injured subject, and can be correlated with other physiological parameters expressing stress.

The VbCG waves "H", "J", "J<sub>2</sub>", and "L" have been shown by Agress (4) to correlate with: the initial rise of left ventricular pressure, the juncture of the slow and rapid phases of isometric contraction, and the opening and closing of the aortic valve, respectively.

The essential interval measures involved are the isometric contraction interval (H-J<sub>2</sub>), and the ejection interval (J<sub>2</sub>-L). These

## THE VIBROCARDIOGRAM

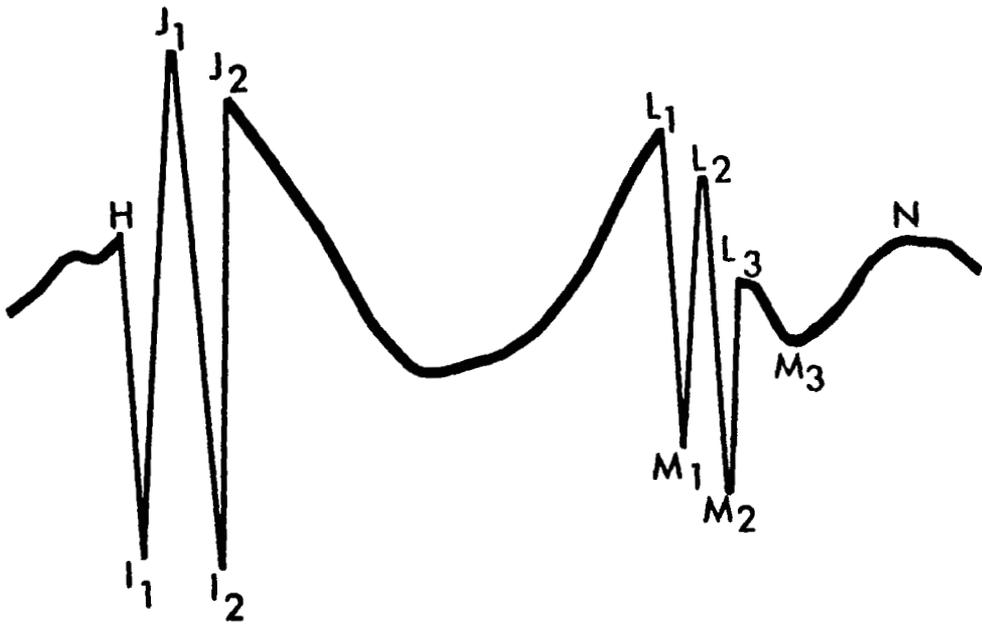


Figure 9

Source: Agress and McInnis (4)

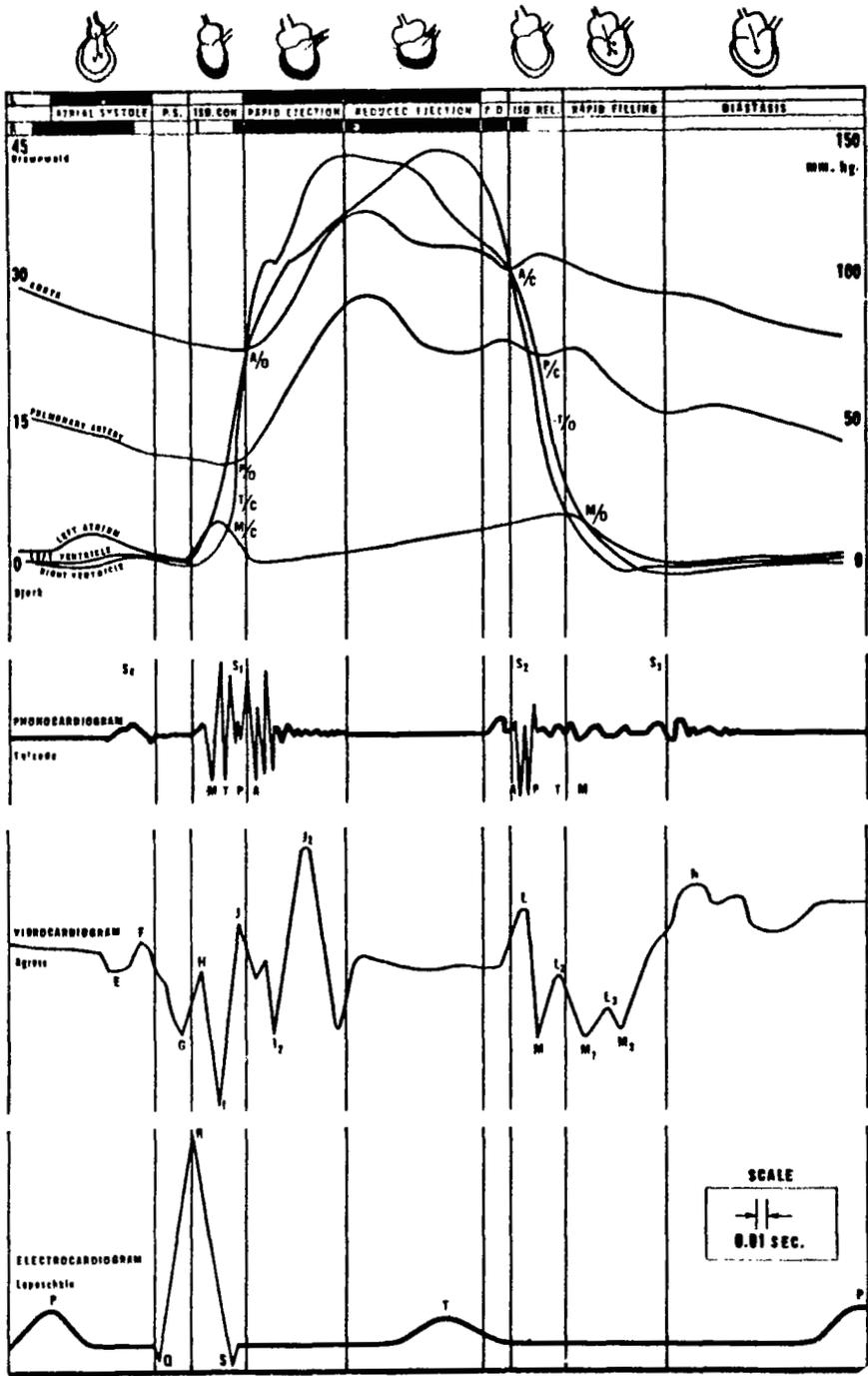


Figure 10

Source: Agress and McInnis (4)

intervals bear a relationship to each other best expressed as the ratio  $H-J_2/J_2-L$ . In normal subjects changes in this ratio parallel  $O_2$  consumption and pulse rate, with an increase after exercise, while in subjects with clinically established heart disease the ratio has been observed to decrease (Agress<sup>(4)</sup>). However, not all stresses act in the same fashion. Proper and Nevison in an unpublished report, found that in normal subjects under hypoxia, the isometric contraction time was reduced, although only to the extent of 5 milliseconds in a 50 millisecond total time, while the above noted ratio was decreased.

Other measures which have been employed in this field include the time-tension index, which is the product of the mean systolic pressure and the ejection time and has been shown to be directly related to myocardial oxygen consumption; the ventricular slope, which is the quotient of the isometric pressure gradient and the isometric contraction time and indicates the rate of development of pressure during isometric contraction; and the mean systolic ejection rate which is the stroke volume divided by the ejection time and indicates the rate at which ejection is occurring. Significant changes have been found in these indices under exercise.

In another area of measurement, Agress<sup>(4)</sup> has developed techniques which he uses for determining cardiac energy level, or mechanical force, and relative stroke volume, from which can be calculated cardiac output. In his work he has shown good correlations with the results of these measures obtained by other methods. In each case, the values are derived from measurements of areas under different portions of the VbCG curve. For energy measures, the entire area under the systolic portion of the curve is used, while for stroke volume measures the area under the ejection phase ( $J_2-L$ ) is employed. Because of the variation in waveform previously noted, and because of doubt as to what the VbCG is actually reflecting, some controversy has arisen over the interpretation of these measures. Lohr et al.,<sup>(200)</sup> in Utrecht, maintain strongly that precordial tracings cannot be used for estimations of cardiac force or stroke

volume. They note the distortion that occurs with various positions of the transducer, and analyze the result of placing the transducer over different areas of the precordium. They recognize four major areas of the precordium: a) the cardiac apex; b) a zone of retraction around the apex where the tracing may demonstrate a mirror image of the apex trace; c) a zone of relative tranquility found especially in the third and fourth intercostal spaces along the left sternal border, and finally, d) the zone of the base of the heart. In each case, however, they find inconsistencies of measurement which preclude the use of that area for the quantitative measurements required. They conclude that... "no area of the precordium would seem to be suitable for the derivation of either stroke volume or the force of cardiac contraction from the accelerographic excursions." In the light of the above, a re-examination and verification of the techniques of Agress in this field would be well justified.

From consideration of all the foregoing, it is apparent that numerous techniques are employed for the investigation of precordial vibrations. This has led to much confusion in nomenclature and interpretation, and there is a tendency to consider that each technique investigates a different phenomenon. This in fact, is not so, and in a timely paper Agress and his colleagues <sup>( 3 )</sup> have examined the common origin of precordial vibrations and have shown that the various records of precordial vibrations represent different attributes of chest wall motion resulting from, and proportional to, the rate of change of pressure within the cardiac chambers. Heart vibration recordings by any technique contain inherently the same information, the graphic differences in the records being dependent primarily on the response characteristics of the transducer and its recording system.

Thus, a displacement transducer responds primarily to the amplitude of the vibrations and is largely independent of frequency. On the other hand velocity transducers have signal output proportional

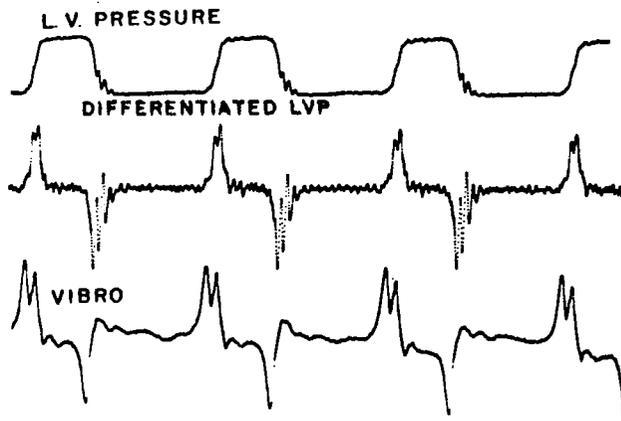
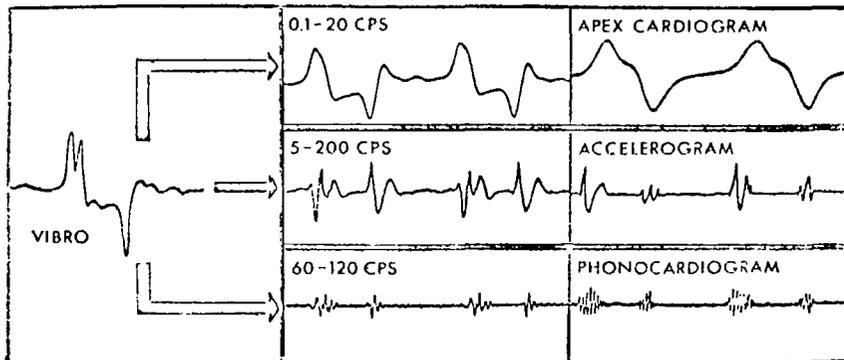


Figure 11

Source: Agress et al. ( 2 )



This figure illustrates the derivation of other types of cardiographic tracings from the vibrocardiogram by use of a variable band pass filter.

Figure 12

Source: Agress et al. ( 3 )

to the frequency of the input, while acceleration transducers have an output proportional to the square of the frequency. Thus, the resulting trace will vary with the transducer used to record it.

At the same time, by use of suitable integrating and differentiating electronic circuitry and band-pass filters, one form of signal can be transformed into another, with, in some cases, remarkable fidelity. Agress et al., ( 2 ) showed that the vibrocardiogram trace could be reconstructed from the first time derivative of ventricular pressure ( Figure 11 ), and in the same paper showed that a trace resembling that of left ventricular pressure could be reconstructed by electronically integrating the VbCG trace.

Similarly, by suitable filtration of the VbCG, traces could be obtained similar to that of the kinetocardiogram (0.1 - 20 cps ), the accelerogram (5 - 200 cps ), and the phonocardiogram (60 - 120 cps) (Figure 12 ). It is perhaps surprising that the accelerogram of Rosa can be obtained by a simple process of filtering when one would expect that integration would be necessary. This may indicate, as already suggested, that Rosa's accelerogram does not truly reflect acceleration, or alternatively that the output of the vibrocardiogram in that range is responsive primarily to the square of the frequency.

However, although all implications and potentialities of the vibrocardiogram are by no means defined, it is obvious that with suitable signal conditioning vibrocardiography provides a simple technique from which a large amount of information on cardiac function can be derived. It should be given strong support as a measure for use in space operation.

As an extension of vibrocardiography, Proper, of the Lovelace Foundation, in conjunction with Ling Temco Vought Western Research Division, is developing a combined vibrocardiograph microphone and miniature accelerometer. With miniaturized band-pass filter circuitry, integrating and differentiating networks, this miniature combined transducer will provide information readable as an apexcardiogram, vibrocardiogram, phonocardiogram, and accelerogram. The accelerometer will provide quantifiable data in terms of G loading, and where the accelerometer is

inactivated by an impressed G field the vibrocardiogram will continue to present useful information. In other situations the electronic circuitry will permit mutual validation of the respective tracings. As a bonus, Dr. Proper observes that the vibrocardiogram microphone will act as a voice back-up should there be a failure in other audio systems. This combined approach would appear to be the most potentially useful of all techniques in the investigation of cardiac kinetics.

### Recommendations

From the above discussion it would appear that useful information can be derived from a study of cardiac kinetics. Three-dimensional ballistocardiography shows very hopeful potential, although much work seems necessary yet in refining instrumentation, collecting baseline data in a nulled gravitational environment, and developing simplified systems of data analysis.

Precordial measurements, which are simpler and require less in the way of instrumentation, seem to be more applicable at this time. Of these, the phonocardiogram has received the greatest attention. It is, however, limited in the range of frequencies encompassed, and when compared with other precordial recording methods, albeit less thoroughly examined, it does not appear to provide so much useful information.

The precordial acceleration tracing and the vibrocardiogram would seem to offer the widest range of information on precordial kinetics, particularly if combined into a conjoined transducer, and provided with suitable electronic processing from which can be derived other precordial traces. The PACT is most advantageously recorded from a miniature strain gauge accelerometer and not from the electromagnetic variety. Further validation of some of the VbCG interpretations would in addition seem to be advisable, particularly with respect to their usefulness in providing measures of, for example, stroke volume, cardiac force.

## SECTION 2

### RESPIRATORY SYSTEM

It is a truism, but at the same time a basic point of reference, to recall that the function of the respiratory system is to accomplish the exchange of gases between the blood and the ambient atmosphere. In some respects, at least, the respiratory system must be examined in association with the pulmonary circulation. The basic respiratory unit is the alveolus, which for proper function must receive a suitable supply of gas and blood. To maintain proper gas exchange the quality and quantity of ventilation must be adequate; relative uniformity of mixing of gas in relation to flow of pulmonary capillary blood must be present; alveolar capillary membrane permeability must be normal; and shunting of venous blood around functional alveolar-capillary units must be minimal. A breakdown in any of these areas will result in impairment of gas exchange, leading to hypoxia and hypercarbia. In addition, there must be satisfactory gas transport between the lung and the other body tissues.

This basic understanding leads to a requirement for anatomical-physiological considerations involving static lung volumes and capacities, the mechanics and dynamics of breathing, the components involved in alveolar gas exchange, and the attributes of blood gas transport.

#### Static Lung Volumes and Capacities

Measurement of static lung volumes and capacities provides the anatomical basis for physiological consideration of other aspects of pulmonary function, and, particularly if trends in change can be observed, may provide an indication of physiological dysfunction, or pathological disorder.

The standard definitions accepted by respiratory physiologists are as follows: (248 )

## Volumes

There are four primary and distinct volumes:

1. Tidal volume (TV): the volume of gas inspired and expired during each respiratory cycle.
2. Inspiratory reserve volume (IRV): the maximal amount of gas that can be inspired from the end-inspiratory position.
3. Expiratory reserve volume (ERV): the maximal volume of gas that can be expired from the end-expiratory level.
4. Residual volume (RV): the volume of gas remaining in the lungs at the end of a maximal expiration.

## Capacities

There are four capacities, each of which is the sum of two or more volumes:

1. Total lung capacity (TLC): the amount of gas contained in the lung at the end of a maximal inspiration.
2. Vital capacity (VC): the maximal volume of gas that can be expelled from the lungs by forceful effort following a maximal inspiration.
3. Inspiratory capacity (IC): the maximal volume of gas that can be inspired from the resting expiratory level.
4. Functional residual capacity (FRC): the volume of gas remaining in the lung at the resting expiratory level. The end-expiratory baseline used here is that established by Christie (60), in contrast with the mid-capacity level that has also been used. The various subdivisions of volume and capacity are illustrated in Figure 13 (247).

Traditionally it has been the practice to measure lung volumes and capacities by the use of water-filled spirometers such as the Benedict-Roth, or in some circumstances, the Tissot. For those volumes that can be measured by direct methods (i. e., excluding residual volume), the subject breathes into and out of the spirometer through a system of valves to establish tidal volume. A deep inspiration is made and expired to resting level for the measurement of inspiratory volume; a full expiration is subsequently made to obtain expiratory reserve volume. Measurement of residual volume is made in another manner which will be discussed later. It is obvious, however, that

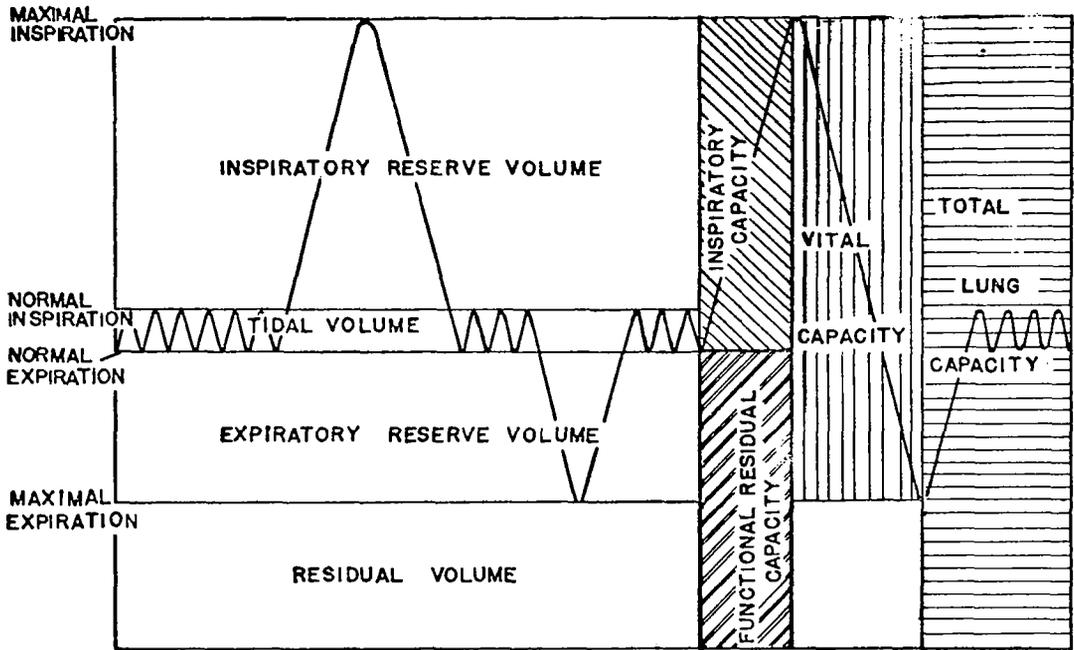


Figure 13. Lung volumes and capacities. Relationship of various subdivisions of lung volume.

Source: Pace ( 247 )

the water-filled spirometer has no place in a weightless environment. Consequently, other techniques for these measures must be considered.

### Dry Spirometry

Several spirometers have been designed which use a gas bellows without a water seal. Notable among these are the Vitalor made by the McKesson Appliance Co., Toledo, Ohio ( 216 ) and the Pulmonor made by the Jones Medical Instrument Co., Chicago, Illinois ( 328 ), each of which is relatively portable and suitable for general survey purposes.

One that has received considerable laboratory attention is the Wedge spirometer, manufactured by Med-Science Electronics, Inc., St. Louis, Missouri. For measurement of volume changes during quiet breathing, a flat response up to 4 cycles per second is adequate ( 34 ), although for rapid volume changes such as those found during maximum voluntary ventilation, devices that respond accurately up to several times that frequency (e. g., 26 cps ) are required ( 214 ). The Wedge spirometer is stated to have excellent response characteristics ( 221 ). With a large surface area and low inertia, it has a high dynamic response, and provides signals proportional to both volume and flow, which can be led off, if required, to a fast-response X-Y recorder, or oscilloscope. Although somewhat large and bulky it could serve a very useful purpose in a space laboratory, if actual spirometry were considered advisable.

The Servo-spirometer, which is also made by Med-Science Electronics, has been suggested for use in space laboratories ( 238 ). The servo-spirometer operates on a mechanism such that when a subject breathes into a cylinder containing a piston, the resulting pressure change activates an electric motor which moves the piston in a direction to compensate automatically for the pressure change. Thus, the pressure in the cylinder remains constant and the movement of the piston is a measure of the volumes and flows of the subject's breathing. There is no doubt that this system would be of value in a space laboratory, but since it is more complex, bulkier and heavier (approximately 70 lbs. and 2 cubic feet ), and provides little additional information, it is doubtful if it would possess any significant

advantages over the less complex and less bulky Wedge spirometer.

### Respirometers

Various types of special purpose respirometers have been devised, such as the Ventube (J. H. Emerson Co., Cambridge, Mass.), and the Wright Respirometer (C. E. Smith, Arlington, Mass.), which are portable and accurate for clinical purposes <sup>( 331 )</sup>, and are suitable for survey purposes. It is doubtful, however, if they have the flexibility and accuracy required for laboratory use.

The Propper spirometer, discussed by Pace <sup>( 247 )</sup>, is a device which works on the rotameter principle, and when properly used is reputed to deliver values comparable to those obtained with the Benedict-Roth. It is, however, open to error, and lacks the flexibility required for laboratory work.

### Bag Methods

The Douglas bag, or special polyethylene bags made for the purpose, can, of course, be used for collection of respiratory samples for measurement of lung volumes. Their advantage, however, is nullified by the requirement for a gas meter or spirometer to measure the sample. For very short missions, however, where few samples are required, the storage of such bags for subsequent measurement might be feasible.

### Pneumotachography

The pneumotachograph was originally developed by Fleisch in 1925 <sup>( 101 )</sup>. Basically it consists of a tube containing a linear flow resistance along with a device for recording the pressure difference across the resistance while gas is flowing through the tube. It follows the principle of Poiseuille's Law, which states that if flow is laminar, the pressure drop along a tube of uniform cross section is linearly related to the flow.

Various components have been used to provide the linear resistance. The original device developed by Fleisch <sup>( 101 )</sup> used parallel tubes and

was bulky; Lilly ( 193 ) utilized a fine mesh screen; while Fry and his associates ( 113 ) at the National Heart Institute employed in one meter a system of vertical plates, and, in another, concentric cylinders. The last named group conducted a comparative study of three different types of pneumotachograph in terms of dead space, linearity, stability of calibration, impedance to respiratory flow, and dynamic accuracy. All demonstrated an acceptable linearity and accuracy of dynamic response (up to 34 cps ); the meter with concentric cylinders, made by National Instrument Laboratories, Inc., Riverdale, Md., had the smallest dead space (41 ml), but lost its calibration after 15 minutes of use; the screen meter, made by Technitrol Engineering Co., Philadelphia, Pa., had the highest dead space (310 ml) but maintained good calibration. One of the factors affecting calibration is the deposit of moisture on the resistance element. In the case of the parallel plate device, moisture is encouraged to drain off the plates by gravitation. Since the gravitational factor will not apply in the weightless state, it may be necessary to prevent the moisture from forming. This has already been approached in the design of screen mesh flowmeters in which an electric current is applied to the screen to increase the temperature ( 303 ).

Another form of pneumotachograph measures gas flow in terms of loss of heat from thermally sensitive resistive device. Heated thermistors are incorporated in a bridge circuit. Heat loss during passage of a gas is determined by the geometry of the device and its components, the number of gas molecules contacting the element, their specific heat, and the temperature differential. The output can be calibrated in terms of volume flow, approximately proportional to the absolute pressure of the gas. The calibration, however, differs with different types of gas, oxygen, nitrogen, water vapor and carbon dioxide. For expired gas measures the calibration has to be based upon expected average concentrations of the different gases. The response time, however, is short, with a time constant of 0.1 seconds, and the overall accuracy is reputed to be within  $\pm 2\%$ . Devices of this nature are made by Technology, Inc., Dayton, Ohio, and by Spacelabs, Inc., Van Nuys, California.

The pneumotachograph, of course, provides a measure of flow. Planimetry of the flow curve, however, gives a measure of volume, or alternatively, application of integrating electronic circuitry can provide a direct readout of volume on the flow trace. The latter is currently being done with success in Luft's laboratory at the Lovelace Foundation, and several integrating systems are commercially available.

### The Flow-volume Loop

As a further modification, flow information from the pneumotachograph can be combined with volume information from a spirometer (or integrating pneumotachograph) to form a flow volume (VF) loop, as originally employed by Hyatt and his associates (162). The loop is obtained by imposing the volume signal and the flow signal on to the X and Y axes respectively of an oscilloscope, or fast response X-Y recorder. A record is made of the loop during a forced maximum inspiratory and forced maximum expiratory maneuver. A resting tidal loop is subsequently registered on the same record, and lung volumes and capacities measured as shown in Figure 14. A calibration device is incorporated into the oscilloscope or X-Y plotter to indicate the deflection occurring for flows of 1 liter per second and volumes of 1 liter. Bartlett (22) utilized this technique to investigate the possibilities of pulmonary function evaluation in space flight. He obtained his volume signals from a Wedge spirometer, or servo-spirometer during his ground studies, but pointed out that for space flight conditions the integrated signal of a pneumotachograph would provide a suitable input.

Other applications of the flow volume loop will be discussed in connection with measures to evaluate the mechanics of breathing.

### Residual Volume, Functional Residual Capacity and Total Lung Capacity

For measurement of most lung volumes and subsequent calculation of most lung capacities, simple spirometry or flowmeter techniques suffice. For measurement of residual volume, however, on which calculation of

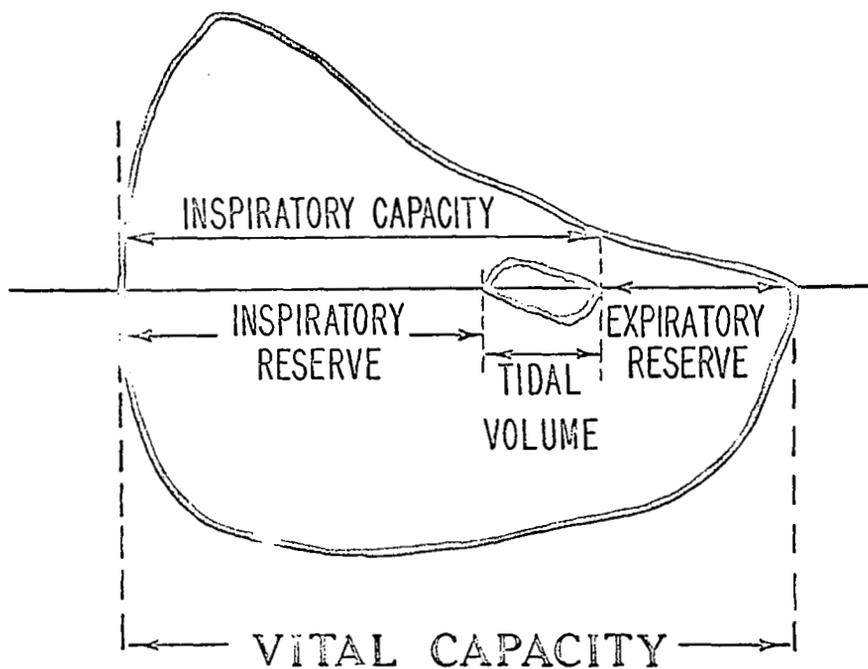


Figure 14. Resting V-V loop superinposed on maximum loop showing use of the loops for obtaining volume values for subdivisions of lung air.

Source: Bartlett et al. ( 23 )

functional residual capacity and total lung capacity depends, a more elaborate approach is required. In fact, under the conditions of an orbiting space laboratory it may not be practicable to make more than an estimate. It might be noted, however, that the postural changes which have been observed in these lung volumes are at least to some extent gravity dependent, and hence changes could be expected in the weightless state.

Two of the most common standard methods of measurement involve either equilibration of a known gas between the lung and an exterior connected circuit, or use of a whole-body plethysmograph. The equilibration systems use either an open circuit technique or a closed circuit technique.

#### Open Circuit Technique ( 74, 75 )

The open circuit technique is based on determining the amount of  $N_2$  in the air-containing lungs at a pre-determined resting level of respiration, and subsequently calculating the volume of air represented by the  $N_2$ , knowing that air comprises 79%  $N_2$ . In an artificial atmosphere of different composition than air, the appropriate nitrogen fraction would be employed. Allowances are made for  $N_2$  concurrently excreted by the body tissues, and for impurities in the oxygen inspired. The technique is achieved by having the patient inspire "pure" oxygen and expire into a large nitrogen-free spirometer. In young healthy subjects the alveolar  $N_2$  is washed out to 1% in about four minutes, but where air trapping or poor ventilation exists the wash-out process may take longer. Seven minutes is generally considered a suitable period, although continuous monitoring will indicate when equilibrium has been reached.

The volume of expired gas in the spirometer is measured, along with its nitrogen concentration. If the volume collected and measured began at the moment of complete expiration, the resulting calculation gives a measure of the residual volume. If it began at full inspiration, the total lung capacity is measured, and if it began at the resting respiratory level, the functional residual capacity is measured.

With respect to feasibility of the technique for space use, nitrogen concentration can readily be measured by a nitrogen meter. Assuming the availability of both oxygen and nitrogen, the major limitation of this method in orbiting conditions lies in the requirements for a large spirometer (commonly a Tissot type) or gas collecting device of perhaps 50-100 liters capacity, plus the complex plumbing. It is possible that gas could be collected in polythene bags and subsequently measured by a gas meter, but the bulk and weight of a gas meter are prohibitive. As an alternative, volume could be measured by expiration through an integrating pneumotachograph.

### Closed Circuit Techniques

Oxygen-Nitrogen: In the early closed circuit technique developed by Christie (60) the subject rebreathed into a closed circuit which included a spirometer containing oxygen. On attaining equilibrium (or, in about 7 minutes) the nitrogen concentration in the spirometer was measured and the functional residual capacity calculated, allowing for tissue nitrogen eliminated, and impurities in the oxygen. The methods, however, led to errors arising from a) changing composition of the inspired gas mixture, b) difficulties in calculation of O<sub>2</sub> consumption from the spirometer, and c) magnification of errors due to small net change in nitrogen concentration (69). Modification led to filling the whole circuit with oxygen and utilizing a blower to ensure mixing (cited by Fowler (105)). The resulting equipment is bulky and complex. Bearing in mind, however, that the errors in the original Christie technique, are more marked in subjects with respiratory disease and that the astronauts are fit, healthy young men, it might be feasible to utilize the original Christie technique with a Wedge spirometer, a nitrogen meter, and a polarographic or other type oxygen sensor which could be available for other purposes, assuming an oxygen-nitrogen atmosphere. The resulting measure would not be as accurate as might be achieved by other means but it would provide a useful comparative reading. In a helium-oxygen atmosphere, the same technique could be used, monitoring helium instead of nitrogen.

Helium Method: To overcome some of the difficulties associated with the Christie technique, McMichael ( 217 ), in addition to maintaining constant spirometer volume by adding oxygen and using a pump to ensure mixing, used first hydrogen and then helium as an indicator gas. In an oxygen-nitrogen atmosphere, the concentration of helium in the lungs is normally zero. If a known volume of helium (e. g., 10% ) is added to a closed circuit of known external volume and equilibration of the helium achieved between the lungs and the external circuit, the resulting concentration of helium in the spirometer, or bellows, of the circuit is the same as in the lung. From the bellows volume and helium concentration, the functional residual capacity can be calculated. Helium concentration can be continuously monitored by thermal conductivity methods or by a mass spectrometer.

From the point of view of use in space, the equipment again is bulky and complex. In addition, in an oxygen-nitrogen atmosphere a source of helium would be required, while in an oxygen-helium atmosphere the technique would not be applicable.

Plethysmographic Method: The whole-body plethysmograph was developed as a valuable technique by Dubois and his colleagues ( 86 ) at the University of Pennsylvania. The principle is based on an application of Boyle's law, by which pressure changes are related to volume changes, provided the temperature remains constant. In practice, the subject sits within a 600 liter airtight box, breathing ambient air through a mouthpiece. To ensure constant temperature conditions, the box is vented periodically to the room outside by means of a solenoid-operated valve until equilibrium is attained. At a given time in the respiratory cycle (e. g. , end-expiration), the mouthpiece is occluded by an electrically operated shutter. The subject is instructed to pant against this obstruction. At end-expiration the alveolar pressure is equal to atmospheric pressure because there is no gas flow. After occlusion, the thorax enlarges with inspiration, decompressing the thoracic gas and creating a new volume and a new alveolar pressure. This new pressure is sensed by a gauge at the mouth behind the occluding shutter,

mouth pressure being considered equal to alveolar pressure under conditions of no flow with the glottis open. Enlargement of the thorax compresses the air around the patient; the pressure change was originally recorded by a sensitive capacitance gauge in the plethysmograph. An unbonded strain gauge is now commonly used. The signal from the mouth pressure is recorded on the vertical axis of an oscillograph and thoracic volume change on the horizontal axis. Panting permits registration of a representative trace from which a slope can be measured:

$$\text{By Boyle's Law: } PV = (P + \Delta P) (V + \Delta V)$$

where  $P$  = pressure

$V$  = volume

$\Delta P$  = change in pressure

$\Delta V$  = change in volume

Knowing  $P$  (atmospheric pressure less water vapor pressure),  $\Delta P / \Delta V$  (slope of the trace) and disregarding the absolute magnitude of  $\Delta P$  which is very small compared to  $P$ , the equation can be solved for  $V$ , the thoracic gas volume, taking into account calibration factors of the plethysmograph. To account for adiabatic compression of gas in the box during panting, a volume of air equivalent to the panting volume is cycled in and out of the box at the panting rate.

With this system, fast and accurate measurements can be made of thoracic gas volumes, which include those volumes not in free communication with the airway. Consequently, this system also measures the volumes of trapped gas and "slow space" gas not normally measured by open or closed circuit techniques.

While it is obviously a method of choice for ground laboratory measurement its application to space laboratories is difficult at this time. Its usefulness for other measures, however, such as airway resistance, pulmonary non-elastic tissue resistance, and pulmonary capillary blood flow, suggest that some consideration should be given to the system.

It is understood that Vorwald of Wayne State is developing a form of "electric field" whole-body plethysmograph, in which the subject, inside a Faraday cage, is exposed to a continuous electrostatic field. Movement of the chest in respiration causes perturbations of the field which can be sensed, amplified, and recorded. The technique, when developed, shows promise for space use.

### Electrical Impedance Plethysmography

The human thorax can be regarded as an electrical volume conductor. As discussed in connection with Cardiac Output, the resistivity ( $\rho$ ) of a homogeneous conducting material, expressed in ohm-centimeters, is related to its resistance ( $R$ ) by the following equation:

$$R = \rho L/A \quad (18)$$

where  $L$  = length in cm., and  $A$  the cross-sectional area in  $\text{cm}^2$ . For a cylindrical conductor the equation, as previously noted, can be written as:

$$V = \rho L^2/R \quad (19)$$

where  $V$  = volume.

In segmental plethysmography, in which the volume changes are attributable to changes in blood flow, the specific resistivity of the blood, namely 150 ohm-centimeters, can be substituted for  $\rho$ . In dealing with lung volumes, however, this factor cannot be applied, since change in volume is not related primarily to blood flow. Allison and his associates (9) have shown theoretically, and by empirical experiment, that the resistivity of the thorax as an electrical volume conductor can be represented by the product of the base resistance and the length between the electrodes determining that base resistance. In other words, the thorax as an electrical volume conductor could be represented as a homogenous cube with a side of a given length. The specific resistivity of such a cube can be measured as the product of the resistance along one side and the length of

that side, provided that with enlargement of the cube the ratio of the length to the cross-sectional area remains unitary. Thus, with a fixed length of side, the specific resistivity of a cube is represented by the resistance along that side, and changes in resistance bear a linear relationship to changes in electrical conducting volume, provided that the length between the detecting electrodes remains constant.

$$\text{Thus: } \frac{\Delta R}{R_0} = \frac{\Delta V}{V_0} \quad ( 20 )$$

where  $R_0$  and  $V_0$  represent the base resistance and initial electrical volume. The initial electrical volume for a given base resistance is represented by a cube of side equal to the distance between the detecting electrodes.

Comparison with spirometer readings showed in Allison's studies that with the upper detecting electrodes across the shoulders, the lower at the level of the 12th rib dorsally, and distance of 30 cm between them, representing a volume of 27,000 ml, measurable changes in resistance could be interpreted as changes in volume. Thus, for example, if the initial resistance were measured at 10 ohms between the detecting electrodes, a change in resistance of 1 ohm with a breathing maneuver would represent a change in volume of 2700 ml. Similarly a change in resistance of 1.8% was equivalent to an average tidal of volume of 500 ml.

Using this principle, Allison et al., ( 9 ) found an error, in comparison with spirometer readings, of 7% or less. At high inspiratory, and forced expiratory volumes, there was less accurate agreement between impedance changes and spirometer volumes. The spirometer values were higher than the impedance changes, perhaps because changes in cross-sectional area are no longer unitary with respect to the fixed length.

As previously noted in the discussion on Cardiac Output, electrical impedance systems are sensitive to subject movement, and, particularly where quantitative measures are being made, require the subject to be at rest. Caranna and his associates ( 53 ) at MacDonnell Aircraft, St. Louis, however, have reported a 2-electrode system with which they can measure tidal volume and lung capacities with minimal distortion regardless of body

position, and even during bicycle ergometer exercise. Their tracings, however, do not reflect the changes associated with cardiac action reported by Allison, and by Kubicek's group (See Cardiac Output). Their system requires initial calibration of the subject's trace with a spirometer. It would seem advisable that if an electrical impedance system is going to be used on the chest that it should be sufficiently flexible for both respiratory and cardiac measurements.

The impedance system can provide usefully accurate measures for the determination of tidal volume, vital capacity, inspiratory reserve volume, and expiratory reserve volume. By pre-calibration on the ground, it may be possible to obtain an index referable to functional residual capacity which could be applied to impedance measures made in orbit.

#### Other Methods

Various techniques have been developed for the measurement of respiration rate, and chest motions associated with respiration. These in the main, have employed devices such as thermistors or thermocouples at the mouth to record changes in temperature with respiration, strain gauges attached to straps around the chest, or Whitney-type mercury-tube transducers fixed around the chest. Rates from these devices can be electronically processed, integrated, and calibrated in terms of volume to provide a reading of tidal volume, but the accuracy of the result is open to question.

Some interesting modifications of these techniques have been reported. Kroboth and Reed <sup>( 178 )</sup> report a device consisting of an elastic rubber cone mask which fits over the nose and mouth and contains a transducer assembly. In the circular opening of the mask are placed three aluminized mylar leaves which move with respiration. A radio frequency signal of 25vRMS at 200 kc is applied to the leaves. Receiving plates are mounted in front of and behind the leaves. Deflection of the leaves modulates the signal received. The resulting signal is processed to register volume of air flow. In addition, the fluctuating air temperature is also recorded and calibrated in terms of air flow, while change in water vapor content is recorded by a system based upon the electrical conductivity of sodium

chloride crystals, which depends upon their moisture content. The dead space of the assembly is only 25 ml. It is not known how well the device performs in comparison with other systems.

Another device, reported by Montoya and Henke ( 226 ) from the Martin Company in Denver, takes cognizance of the fact the restrictive bands around the chest may alter the pattern of breathing. To overcome this artifact they developed a system which utilizes two strain gauges, one mounted on each of two flexible plastic tubes and held in place against the chest by a snugly fitted elastic chest band. One tube is mounted vertically over a pectoral muscle and one over a corresponding scapula. Movement of the chest deforms the elastic tubes and is recorded by the strain gauges. Methods of measurement involving chest movement are satisfactory for respiratory rate registration, but when used for the estimation of volumes they fail to take into account the contribution of diaphragmatic movement and abdominal breathing.

### Recommendations

For the measurement of lung volumes and capacities in orbital conditions there would seem to be three major approaches. The technique combining the greatest simplicity, scope, and reliability would appear to be the use of the integrating pneumotachograph with display on an oscilloscope or X-Y plotter. Considerable validation of the method, however, is still required on the ground, and even more so under weightless conditions. In the latter case in particular, experimentation is desirable to develop a method to reduce possible interference occurring from the accumulation of water vapor. Should actual spirometry be required, and it is difficult to see any advantage of spirometry in routine use, a bellows-type Wedge spirometer with X-Y display would seem to be suitable. It is probable that the size of the existing equipment can be reduced still further without great loss in reliability. Electrical impedance pneumography also deserves consideration, particularly as a back-up, for example, for the pneumotachograph, and for prolonged intermittent, or continuous traces.

The essential simplicity of the instrumentation and minimal subject violation assist in outweighing the disadvantages that might accrue from motion sensitivity.

The whole-body plethysmograph, however, cannot be summarily dismissed, simply because of its bulk. There is little doubt that this device provides the most accurate, reliable, and comprehensive measurement system for lung volumes and capacities and for other aspects of respiratory investigation. While its use for routine respiratory measurement in a space laboratory could not be reasonably justified, a portion of a spacecraft could be modified for such use in a special purpose mission if the need became manifest. In a large manned orbiting laboratory it would seem possible, for example, that an airlock could be modified for this purpose.

The problem of measurement of residual volume and functional residual capacity remains difficult, largely because of the bulk and plumbing complexity of the necessary apparatus. In an oxygen-nitrogen atmosphere, perhaps the most feasible, if not the most accurate, method would be a closed circuit method using a Wedge spirometer or integrating pneumotachograph, and analyzers for oxygen and nitrogen. In an oxygen-helium atmosphere, the helium could be similarly analyzed. Closed circuit methods employing helium or hydrogen as indicators in an oxygen-nitrogen atmosphere do not lend themselves to space cabin use because of the requirement for a source of helium. There is a possibility, however, as noted earlier, that an index of functional residual capacity, or residual volume, may be obtained by the technique of electrical impedance plethysmography, although further validation is required before final recommendation can be made.

## MECHANICS AND DYNAMICS OF BREATHING

Measurements of lung volume, although valuable for baseline information, provide minimal information on the mechanics and dynamics of breathing. In the weightless state, and particularly in the presence of artificial atmospheres and perhaps even contaminated atmospheres, changes might be expected, and it would seem advisable to undertake measures indicating the nature and trend of any change. Measurements involve overall assessments of mechanical function, pressure, and volume, to determine the compliance, and airway and tissue resistances. Some of the techniques can be applied with little problem. Some are demanding in equipment and subject cooperation.

### Flow-volume Relationships

The measurement of dynamic lung volumes provides an overall assessment of the efficiency of the mechanical function of the pulmonary system and involves the relationship between air flow and changing lung volume.

Hyatt ( 161 ) in his review, notes that essentially two types of measures are made, although numerous names and techniques have been applied to subdivisions of the measures. One measure involves aspects of the forced vital capacity (FVC) maneuver, and the other arises from the maximum breathing capacity (MBC) test.

In the FVC maneuver the subject exhales as rapidly and completely as possible after a maximum inspiration. It has been shown ( 113, 162 ) that at lung levels near total lung capacity there is no physiologically defined limit to respiratory flow and consequently maximal flow is related to maximal effort. At volumes below two-thirds of vital capacity, however, maximal flow values decrease with the level of lung inflation, and increased effort actually reduces flow slightly, because of increased constriction of the conducting airways from the increased transpulmonary pressure. There are no fixed maxima on inspiratory flow, and it again would appear to be effort dependent.

From these findings it may be inferred that firstly, maximal expiratory flows are a function of lung inflation, and consequently that volumes at which flows are measured must be specified; secondly, flow-volume relations over the lower two-thirds of vital capacity are not prone to subjective variability and hence are readily reproducible.

These considerations have led, both empirically and on theoretical analysis, to various methods of quantifying the FVC maneuver, as illustrated in Table 6, which is modified by Hyatt ( 161 ) from the work of Gandevia and Hugh-Jones ( 119 ). Traditionally the FVC maneuver is performed by having the subject breath into a fast-recording spirometer, which produces a volume-time trace of the forced expiration, from which various timed volumes and flow rates can be extracted. The disadvantages of spirometers for use in space conditions have already been discussed. The same maneuver, however, can be recorded with an integrating pneumotachograph. Hyatt ( 161 ) points out that the flow versus volume plot provides even more useful information than the flow versus time, and observes that, if necessary, the former can readily be converted into the latter by numerical and graphic manipulation, or by electronic means. The integrating pneumotachograph, which is primarily a flow meter, provides the necessary information for the plot when the volume signal is placed on the X-axis of an oscilloscope or X-Y plotter, and the flow signal on the Y-axis. The resulting trace is illustrated in figure 15 ( 161 ). This figure also indicates the method of deriving a volume-time trace from a volume-flow trace by taking small increments of volume (e. g., 0.2 liters), determining a flow rate for each increment, calculating the time, and transferring it to the time-plot. The figure further illustrates the positioning of different measures on the trace, as will be discussed.

The measures listed in Table 6 which can be derived from this trace include timed volumes, mean maximal flow rates; maximal flow rates at a given point in expiration, and peak flow rates. The absolute volume of the forced vital capacity has also been used as a measure.

Table 6. Proposed Nomenclature

	Description	Recommended Term	Abbreviation	Some Previous Terms
1	Maximal volume measured on expiration after the deepest inspiration	Vital capacity	VC	
2	Maximal volume measured on inspiration after a full expiration	Inspiratory vital capacity	IVC	
3	Spirogram of a forced, complete inspiration or expiration	Forced inspiratory/expiratory spirogram	FIS/FES	Fast inspiratory/expiratory vital spirogram; expirogram
4	Volume of gas exhaled over a given time interval during a complete forced expiration	Forced expiratory volume, qualified by time interval used in sec	FEV <sub>T</sub>	Timed vital capacity; fast expiratory capacity; forced expiratory volume; capacity usable on effort (Fr. CPUE); maximum expiratory volume (Fr. VEMS)
5	Volume of gas expired after full inspiration, expiration being as rapid and complete as possible (i.e., forced)	Forced vital capacity	FVC	Timed vital capacity; fast vital capacity; fast maximum expiratory capacity; forced expiratory vital capacity
6	FEV <sub>T</sub> expressed as % of VC or FVC*	Percentage expired qualified by time interval used in sec	FEV <sub>T</sub> %	Timed vital capacity; timed expiratory capacity; optimal frequency (Fr.)
7	Peak expiratory flow (liters/min or liters/sec) measured by various instruments	Peak expiratory flow qualified by name of instrument used	PEF	
8	Volume of air exhaled over a specified volume range of the FES divided by the time to exhale this volume, expressed as liters/min or liters/sec	Mean maximal expiratory flow qualified by volume range in liters or as % of the FES		
	Examples:			
	A. Volume between 0.2 and 1.2 liters of the FES/time	Mean maximal expiratory flow, .2-1.2 liters	MMEF <sub>.2-1.2L</sub>	Maximal expiratory flow rate (MEFR) (15)
	B. Volume between 25 and 75% of the FES/time	Mean maximal expiratory flow, 25-75% of FES	MMEF <sub>25-75%</sub>	Maximal midexpiratory flow (MMF) (61)
	C. Volume between 50 and 75% of the FES/time	Mean maximal expiratory flow, 50-75% of FES	MMEF <sub>50-75%</sub>	Expiratory rate during third quarter of a maximal forced expiration (E <sub>50-75</sub> ) (35)
9	Maximal expiratory flow at a specific volume during a complete forced expiration, expressed in liters/min or liters/sec†	Maximal expiratory flow qualified by the volume at which measured, expressed as % of the FVC exhaled		
	Examples:			
	A. Flow at point when 25% of FVC exhaled	Maximal expiratory flow, 25% of FVC	MEF <sub>25%</sub>	
	B. Flow at point when 50% of FVC exhaled	Maximal expiratory flow, 50% of FVC	MEF <sub>50%</sub>	
	C. Flow at point when 75% of FVC exhaled	Maximal expiratory flow, 75% of FVC	MEF <sub>75%</sub>	

\* The method of measuring the vital capacity should be indicated by use of VC or FVC in the denominator. Thus,  $FEV_{15\%} = \frac{FEV_1}{VC} \% \text{ or } \frac{FEV_1}{FVC} \%.$

† Such values can be read directly from a flow-versus-volume plot of an FVC maneuver.

Note: Should one want to quantify a forced, complete inspiration, this could be designated by substituting "I" for "E" in items 4, 6, 8 and 9. Item 5 in this case would be designated forced inspiratory vital capacity or FIVC.

Source: Hyatt ( 161 )

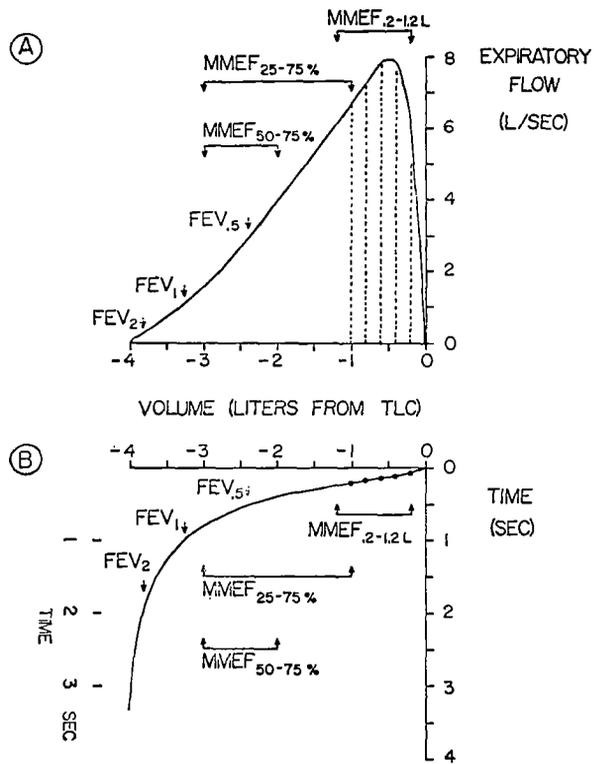


Figure 15. A: FV plot of an FVC maneuver from a normal subject.  
 B: the derived volume-time trace of the same breath.

Source: Hyatt ( 161 )

### Timed Volumes

Timed volumes refer to the volumes of gas expired during various increments of time. Essentially, timed volumes obtained from a spirometer are a substitute for flow measures. Utilizing the slope of the spirometry curve over a given time or volume range, an average flow for that range can be obtained. Various times have been used, from 0.43 to 3.2 seconds, although common durations are 0.5, 1, and 2 seconds. These points are noted in figure 15. Since volumes measured from the start of expiration include considerable variation in flow, from zero to peak, and since, as noted above, the first third of expiration is effort dependent, it is probably better to select a starting point after the beginning of expiration, and measure a given volume therefrom. Selection for this purpose has included the range from 0.2 to 1.2 liters, but perhaps it would be still better to measure over the range from 25% to 75% of the volume, or even 50% to 75%, where the flow is more readily reproducible. Timed volumes are most easily obtained from a volume-time trace, but can be derived from the pneumotachograph volume-flow trace either manually or after electronic processing. Special automatic spirometers are available for timed volume measures, such as those used by Gaensler ( 116 ), Wright and Gilford ( 349 ), and others. It is also possible to exhale through a wide-bore valve into a collecting bag and time the exhalation with a stopwatch. The special purpose spirometers, however, are unsuitable for space use, and the bag collection method is obviously open to great error and provides no continuous record.

To reduce variations associated with age, size, and sex, the results of timed forced expiratory volumes may be expressed as a per cent of the vital capacity or forced vital capacity, although in interpretation it must be borne in mind that both the numerator and denominator can be proportionately reduced and present an apparently normal index.

### Maximal Flow Rates

Maximal flow rates, which may refer either to mean maximal flows over a range of volume, or to maximal flow rates at a given level of volume, can be read directly off the volume-flow trace. Some ranges are illustrated in

figure 15. Common ranges for measurement of a mean are from 0.2 to 1.2 liters, or perhaps preferably from 25% to 75%, or 50% to 75%, of the expiratory volume. Suggested points of measurement for maximal flow are at the 25%, 50%, and 75% levels of expiratory volume. Hyatt ( 161 ) quotes a personal observation of Lloyd and Wright, who found in a small group of normals that measurement of maximal expiratory flow at a volume of 1 liter above residual volume was not so useful as that taken at 50% of expiratory volume., and suggests accordingly that maximal expiratory flow measurements near mid-vital capacity may be superior to those made at very low volume.

### Peak Flow Rate

Peak flow rate can also be measured from the volume-flow trace. Peak flow rate, however, is inherently dependent on the subject's effort, and on the level of the initial lung volume. Consequently measures must be made after a maximal inspiration. Several instruments have been devised for use in peak flow measurements as a screening test. Notable among these are the Wright flow meter and the Puffmeter.

The Wright flow meter ( 350 ) has received wide acceptance as a screening device. Air entering the meter displaces a rotary vane against a spiral spring which progressively uncovers an orifice according to the extent of displacement of the vane. The deflection of the vane, modified by the tension of the spring, is proportional to the air flow. An exterior pointer attached to the vane registers the flow rate on a dial. The instrument can be held in the hand and weighs about 2 lbs. After full inspiration, measures are made by exhaling forcibly into the device. Comparisons with peak flows measured by a pneumotachograph have showed good agreement ( 350 ). Lloyd and Wright ( 198 ) also undertook an evaluation of this meter but found it overestimated by about 10% between flows of 200 to 500 liters per minute as compared with a pneumotachograph. there is little doubt that it is a valuable instrument for screening purposes, but its use in space would seem unnecessary if other apparatus such as an integrating pneumotachograph were available.

The same consideration would apply to the Puffmeter ( 130 ). The

Puffmeter is a form of rugged, portable pneumotachograph in which the resistance is made from a porous, vitrified, cup-shaped, grinding wheel. An attached pressure gauge is calibrated in terms of air flow rate. Goldsmith ( 130 ) found a high correlation (0.992) between values found with the Puffmeter and with a standard screen pneumotachograph. The instrument has been extensively used in screening tests in detection of persons with pulmonary air flow obstruction.

### Maximum Breathing Capacity

The maximum breathing capacity (MBC) is the maximum volume of gas that can be breathed in a given time (usually standardized per minute). The maximum voluntary ventilation (MVV) is the maximum volume that can be breathed by voluntary effort. In the normal healthy cooperative subject the two should be identical. The MBC is commonly recorded on a spirometer for 10-30 seconds, but special high frequency response, fast recording spirometers are necessary for accurate results ( 34, 338, etc.) and are unsuitable for space use.

The test can also be undertaken by breathing through a low resistance valve (e. g. , a Rudolph valve) into a Douglas bag, or similar collecting device, and subsequently measuring the gas delivered in a given time. The disadvantage of Douglas bag collections has been discussed.

Useful measures, however, can be made from the flow-volume loop. Bartlett and his colleagues ( 24 ) observed that when an MVV loop is superimposed on a flow-volume loop it follows the maximum envelope during the major portion of a breath half-cycle until it breaks away abruptly, transects the zero velocity abscissa, and rejoins the maximum envelope for another half-cycle. Because of this relationship they simulated an MVV loop by erecting perpendiculars at each end of several assumed tidal volumes, and calculated the time for moving each assumed tidal volume on the basis that the time equals the square of the volume divided by the area. Optimum placement of the tidal volume is found by determining from a family of curves derived from the flow-volume plot the optimum limit of inspiration for a given

breathing frequency. The predicted MVV by this method compares favorably with the predicted MVV obtained by spirometer. Bartlett suggests that the predicted MVV might well be used as an index instead of the measured MVV.

Still another technique for measuring the MBC was devised by Warring and Siemsen ( 332 ) using an instrument, the Ventube, based on the Venturi principle. The Ventube is a cylinder with an internal diameter which becomes progressively smaller from each end towards the middle. A single side-arm at the throat is connected to a balloon filled with a known volume of air. On rapid breathing through the tube, air is aspirated from the balloon in quantity proportional to the volume of air passing through the tube. In practice the balloon is filled with about 500 cc of air by way of a 100 cc syringe, the tubing clamped, and then fitted to the Ventube side-arm. The clamp is opened and an MBC maneuver carried out for 15 seconds. The tube is again clamped and the volume of air remaining in the balloon is measured in a standard manner by the 100 cc syringe. The volume of aspirated air is calculated, and the breathing volume which it represents is obtained from conversion tables. Good agreement has been found between results obtained by this method and by other methods, such as the use of a Douglas bag and Rudolph or Collins valve, or by spirometer.

Although it is obviously a valuable and simple technique, again it is doubtful if the additional equipment is desirable in a space laboratory.

#### Volume Displacement Plethysmography

Volume displacement plethysmography has been used for the evaluation of flow volume relationships ( 219 ). The volume displacement plethysmograph, in contrast with the pressure-sensing plethysmograph, is used to measure volume change in breathing by way of an attached exterior Krogh spirometer which follows the motion of the chest cage. Flows can be obtained by electronic differentiation of the volume signal or from a pneumotachograph in the breathing circuit. The bulk and complexity of the apparatus, however, make it an unnecessary luxury for space laboratory conditions.

## Pressure-volume Relationships

The muscular force of inspiration is required to overcome the elastic recoil of the lungs and thorax, the frictional resistance that arises during tissue movement of the lung and thorax, and the frictional resistance of the conducting airways. The elasticity of tissues of the lungs and thorax is demonstrable in terms of the relationship between pressure and volume, measured under static conditions in the form of compliance. Compliance is the change in volume per unit change in pressure (L/cmH<sub>2</sub>O). By Hooke's Law, the relation between volume and pressure, or stretch and force, is dependent on the change in volume or distance. The slope of the line of relationship between the two is a measure of the compliance.

Measurement of pulmonary compliance ideally requires a measure of the transpulmonary pressure, i. e., the pressure differential between the intrapleural space and the mouth. Under most circumstances this is an impracticable measurement, and intraesophageal pressure is used instead.

Various methods of obtaining esophageal pressure measurements have been discussed by Mead et al., all based upon the passage of a small-bore rubber catheter through the nose into the esophagus. Sealed to the esophageal end of the catheter is a thin walled rubber balloon. The system is filled with air, and the reflected pressure changes within the balloon are observed by an inductance type manometer. Another modification utilizes an open-ended catheter. In this case, the catheter and the recording system are filled with water and the pressure changes recorded by a capacitance manometer. It is necessary for the system to be responsive to frequency components up to about 10 cps.

Different sizes of balloon have been used, varying from about 3 cm long by 1 cm in diameter ( 222 ) to 18 cm long by 1 cm in diameter ( 115 ). Mead et al., ( 222 ) showed that, overall, the long-balloon possessed advantages over the short-balloon, and over water filled catheters. In any event, a water filled system would be unsuitable for space use.

Still another system utilizes a miniature pressure transducer mounted

directly on the tip of the catheter, as has been suggested by Gauer and Gienapp ( 123 ) and used by Lim and Luft ( 197 ). Concurrent volume measurements can be made from a spirometer or an integrating pneumo-tachometer.

Although pulmonary compliance is a static measure representing the elastic recoil of the lungs, in practice it is measured in either static or dynamic conditions. In the normal subject static and dynamic compliance should be nearly identical. In the static measurement the subject inspires a measured volume and holds his breath with the glottis open for a pressure measurement, repeating the procedure for several different volumes. A pressure volume curve is constructed from the measures, with the average compliance of the lungs being read as the slope of the curve. The slope is usually constant over the range used, although not so at extremes of the vital capacity.

Compliance measurements can also be made by the use of an interrupter technique ( 112 ) whereby an electronically operated shutter interrupts the air flow at various lung volumes during respiration. At the moment of no flow, the transpulmonary pressure rapidly reaches a steady state, which is recorded on the manometer in relation to the lung volume at that time.

An alternative method of making dynamic measures was propounded by Neergard and Wirz, ( 233 ), and is based on the fact that at the moment between the beginning of expiration and end of inspiration there is no flow, and consequently, no pressure against flow resistance. Thus, transpulmonary pressure at that time represents pressure against the elastic recoil of the lungs.

With suitable techniques of obtaining continuous pressure and volume, compliance is most readily measured from a pressure-volume trace on an oscilloscope or X-Y plotter as the slope of the line joining the points of zero air flow.

In clinical conditions where the linearity of the relationship may be modified by the non-elastic resistance of the airflow the effect of the latter

can be removed electronically from the pressure signal by "bucking" the pressure signal with an electric signal proportional to airflow ( 211 ).

Interpretation of compliance values must take into account the lung volumes at which the compliance is measured. It is common to relate it to the FRC. Compliance measures show a postural change along with the FRC. Both compliance and FRC are reduced in changing from the erect to the supine position. The relationship between them, however, remains unaltered ( 197 ). The FRC in turn is dependent on the size of the lung and on the balance between the retraction of the lung and the expansion of the chest wall. Marshall and Widdicombe ( 212 ) point out that compliance measurements made during normal tidal volume, but at lung volumes considerably above or below FRC, may give low values because of the effects of stress relaxation. They consequently recommend that measures be made on breaths inspired from the FRC.

It is apparent that under space laboratory conditions the major limiting feature in compliance measurement lies in the subject violation imposed by the requirement to swallow an esophageal catheter inserted through the nose. While the procedure is neither hazardous, nor even unduly uncomfortable, it does seem formidable to the inexperienced subject. There is, however, no less complex way by which a measure can be obtained representative of transpulmonary pressure. Consequently, if it is considered necessary to make compliance measures, (and because of the changes that can be expected with weightlessness it would seem advisable), experienced subjects and investigators will be necessary. Experience, of course, will be gained through the necessity of establishing pre-flight baseline values.

It would seem that the technique combining the least bulk and complexity with the greatest reliability would involve the continuous recording of respiration volume by way of an integrating pneumotachograph, and concurrent registration of intraesophageal pressure from a pressure transducer mounted on a catheter tip, and subsequent display of the respective values on an oscilloscope or X-Y plotter.

The compliance of individual lungs can be measured during broncho-

spirometry. The latter, however, would appear to be an unnecessary imposition for space laboratory conditions, unless under exceptional circumstances.

### Compliance of Lung-thoracic Cage System

Measurements of compliance of the lung-thoracic cage system require a measurement of transthoracic pressure. The most satisfactory method to obtain a measure of this pressure is the use of a body respirator in an unconscious or paralyzed subject, a technique obviously not practicable in a manned space laboratory.

The relaxation method of Rahn et al. ( 264 ) has also been used. In this technique, after inspiration of a given volume of air, the subject closes his nose and mouth, opens his glottis, and relaxes his chest muscles. Trans-thoracic pressure is measured by a nasal tube in the nostril. Repetition at different volumes produces a relaxation pressure curve. Consistency in results is difficult to achieve, however, and a trained and experienced subject is required to complete the maneuver satisfactorily.

### Pressure-flow Relationships

There are two components of non-elastic resistance, one related to airway resistance and the other to pulmonary and thoracic tissue, or viscous, resistance. Airway resistance is represented by the alveolar pressure divided by the flow rate at that pressure.

The relationship between pressure and flow can be expressed in quadratic form:

$$P = K_1 \dot{V} + K_2 \dot{V}^2 \quad ( 21 )$$

where  $K_1$  and  $K_2$  are constants representing an association with laminar flow and turbulent flow respectively. Thus, the relationship is non-linear, and although curves can be obtained describing the relationship at different flow rates, resistance measured at 0.5 liters per second is taken as being a representative measure of resistance during normal breathing ( 211 ).

For actual measurement under dynamic conditions, values relating to the flow rate at the mouth and the transairway pressure are required. The latter is the pressure difference between the alveoli and the mouth. The whole body pressure-sensitive plethysmograph, along with a heated pneumotachograph ( 85 ) provides the most direct measurement. The subject, inside the plethysmograph, breathes through a pneumotachograph and an interrupter valve. The flow meter is heated to prevent condensation of water vapor, and consequently breath volume is limited to the capacity of the flow meter system (about 300 ml). The subject therefore pants. Panting, however, serves to magnify volume displacements during variations of alveolar pressure, and minimize other interfering factors associated with changes of temperature, water vapor pressure, and varying exchange of  $\text{CO}_2$  and  $\text{O}_2$  in the lung.

On inspiration, alveolar volume is increased, thereby reducing alveolar pressure. The change in volume is reflected as a change in pressure by the sensitive plethysmograph manometer. Changes in airflow are plotted simultaneously against plethysmographic pressure changes, which are proportional to alveolar pressure changes. Immediately subsequent, the interrupter is closed and a plot obtained of mouth pressure (alveolar pressure) and plethysmograph pressure. This provides a calibration of alveolar pressure in terms of plethysmograph pressure. Airway resistance can then be calculated from the respective alveolar pressures and flows.

Problems associated with whole-body plethysmography in orbital conditions have already been discussed. If such a device can be made available, however, it would provide an invaluable method of determining airway resistance measures. The volume displacement whole-body plethysmograph has also been used for the purpose ( 163 ).

In a review of the subject of non-elastic resistance, Marshall ( 211 ) discusses other means of obtaining measures, in the absence of a plethysmograph, using continuous pressure and flow tracings from a pneumotachograph with a pressure read-out. At a given rate of flow (e. g., 0.5 liters per second) the non-elastic resistance can be calculated by subtracting from the total pressure difference at that rate the component exerted against elastic

resistance. The latter can be obtained from a concomitant measure of compliance. Non - elastic resistance calculated in this manner includes elements of pulmonary and thoracic tissue resistance.

Still another method utilizes the information from pressure-volume traces, whereby two points of similar lung volume are selected, one on inspiration and the other on expiration, and the pressure differential occurring between these two points is obtained from a concurrent pressure trace. The flow rate at these two points is determined from the slope of the volume trace, and the non-elastic resistance is found by dividing the pressure differential by the sum of the flow rates at the two points.

Perhaps the most elegant system, using electronic processing of the signals, was developed by Mead and Whittenberger ( 222 ). The flow signal from a pneumotachograph is placed on the Y-axis of an oscilloscope or X-Y plotter, and the intraesophageal pressure on the X-axis. Assuming that the pressure exerted against elastic resistance is proportional to the volume inspired, a signal proportional to the volume inspired is also applied to the X-axis in the opposite vector to that of the pressure signal. This volume signal is so adjusted as to close the pressure-flow loop and form a more or less straight line. With the loop closed, the pressure recorded at the beginning and end of inspiration (zero airflow) is the same. The slope of the line provides a measure of non-elastic resistance. The "quality" of the line is improved by panting, although under these circumstances the resistance is lowered.

Methods of measurement of non-elastic resistance utilizing a shutter to interrupt the airflow in a pneumotachometer were developed by Neergard and Wirz ( 234 ) in conjunction with their compliance measures, on the principle that when airflow is stopped the pressure equalizes rapidly between the alveoli and the mouth proximal to the shutter. Although the pressure so measured at the mouth includes conversion of some of the kinetic energy of the lungs and chest wall into pressure, the resulting measure provides a good approximation of alveolar pressure. By making several measures during a respiratory cycle, the non-elastic resistance can be derived from the ratio of pressure to flow. This method, however, is not widely accepted.

Clements and Elam ( 63 ) modified the method for continuous reading by devising a rotary airflow interrupter with a motor-driven chopper and pressure gauges. In an evaluation of the instrument, however, Lloyd and Wright ( 198 ) found considerable variation in results, both in consecutive measures, and in comparison with whole body plethysmography.

Pulmonary viscous resistance does not lend itself to independent measurement. A value, however, can be obtained by measuring total non-elastic resistance, e. g., as obtained from pressure and flow measures, and subtracting from that the airway resistance as obtained by the whole body plethysmograph.

For orbital space laboratory conditions, then, it would seem that the most reliable information on pressure-flow relationships, airway and pulmonary resistance would be forthcoming from a whole-body pressure sensitive plethysmograph. Valuable information, however, can be obtained from less bulky and cumbersome devices. If measures of intraesophageal pressure are going to be made for compliance studies it would be appropriate to combine the compliance measures with pressure and flow studies, using the subtraction method of Mead and Whittenberger ( 222 ) previously discussed. If, however, measures of esophageal pressure are considered inadvisable (and there does not appear to be good reason to consider them as such with experienced persons) then good indications of non-elastic resistance can still be obtained from flow and volume curves, or by a repetitive interrupter method as described.

At the same time, consideration should again be given to the development of a suitable whole-body plethysmograph for use on special missions.

### Work of Breathing

Work in the physical sense is the product of force and distance, or pressure and volume. Thus,  $W = \int P dV$

In the respiratory system work is involved in overcoming elastic

resistance, airway resistance, and in moving the lungs and thoracic cage. Thus, the work involved in overcoming elastic recoil of the lungs, airway resistance, and non-elastic pulmonary resistance, can be calculated from a trace of transpulmonary pressure against volume, as the area bounded by the inspiratory curve and the ordinate, when volume is placed on the ordinate. The area bounded by the ordinate and the diagonal joining the points of beginning and end inspiration represents the work of overcoming elastic recoil; the remainder represents the additional work of moving non-elastic tissue and overcoming airway resistance.

The work of moving the thoracic cage does not lend itself to measurement in orbital space laboratory conditions. In respiratory paralysis, deep anesthesia, or neuromuscular block of the respiratory muscles, when ventilation is maintained by a body respirator, the work can be calculated from simultaneous measurements of transthoracic pressure, *i. e.*, the pressure differential between the mouth and the inside of the respirator with inspiration, and the volume of gas moved during inspiration.

The  $O_2$  consumption during different levels of exercise also provides an index of work performed. The  $O_2$  consumed, of course, includes both that required in doing external work and in increased respiratory work. This measure can be obtained in several ways using a waterless spirometer or Douglas bag, but in accordance with earlier discussion, the use of the integrating pneumotachograph would appear the most satisfactory. In this situation, one flow meter would be required to measure the volume of inspired gas over a given period of exercise while another, through appropriate valving, would measure the expired gas. The volume of inspired  $O_2$  would be calculated from the partial pressure of  $O_2$  in the inspired air. The  $O_2$  concentration in the expired air would be derived from the output of a rapid response  $O_2$  sensor. The difference between the inspired and expired  $O_2$ , of course represents the  $O_2$  consumption. Kissen and McGuire (172) have recently presented instrumentation to achieve this end.

Spirometric and Douglas bag methods would necessitate collection of the gas and subsequent analysis by other methods such as by mass spectrometry or gas chromatography.

## RESPIRATORY GAS ANALYSIS

It is apparent that traditional methods of respiratory gas analysis employing the Scholander or Haldane type of apparatus will not be applicable in space conditions, dependent as they are on manipulation of fluid levels. It is, thus, necessary to consider other methods of measurement of the volume and partial pressure of respiratory gases, including in particular, oxygen, carbon dioxide, nitrogen, and perhaps helium.

The study undertaken by Beckman Instruments, Inc., on behalf of the U. S. Air Force includes valuable information in this field, particularly with respect to the development and uses of spaceborne gas chromatography and mass spectrometry. Another very helpful general review, without particular application to space use, is by Severinghaus ( 295 ).

One of the most useful devices for this purpose, when it is functioning according to its specifications, is the mass spectrometer. Mass spectrometers have been looked at askance by various respiratory physiologists. Foster of the University of Pennsylvania (personal communication) states: "This is a finicky, delicate instrument on earth. Its percentage accuracy for a given sample is only of the order of a percent. Its greatest power is in its ability to analyze small total amounts of material. In the case of respiratory gas analysis there is usually plenty of sample; the need is for accuracy to three places. There are corrections, often arbitrary, depending on different particular instruments. . . . Although the use of a mass spectrometer for respiratory analysis in space is intriguing, I wonder if the actualities of its accuracy have been considered. Actually the major reason that I can see for using one is the availability of free vacuum." Despite Foster's comments, the mass spectrometer has been used in various laboratories with considerable success, including that of Luft in the Lovelace Foundation, where the accuracy is considerably better than 1%, and also in the X-15 aircraft by the NASA Flight Research Center at Edwards. It has an additional advantage of permitting continuous on-line readout.

Essentially there are three types of mass spectrometers, the magnetic analyzers (Consolidated Systems Corporation), the time-of-flight mass

spectrometer (Bendix) and the coincidence mass spectrometer (Garrett AiResearch). In each case the sample is first ionized by a stream of electrons in an ionization chamber. In the magnetic analyzer, the resulting beam is tightly collimated and passed through an applied magnetic field, which causes the ions to bend out of their original linear path. Dependent on the change to mass ratio, the ion path is curved to a greater or less degree, and provides separation of the ions which are collected and counted on specific collector plates.

In the time-of flight mass spectrometer, the ions are exposed to a pulsed radio frequency source, which imparts kinetic energy to them proportional to their molecular weight. They are then accelerated towards a detector, and since the velocity derived from the kinetic energy is dependent on the mass, the lighter ions reach the detector earlier than the heavier. The time of flight provides a measure proportional to mass.

In the coincidence spectrometer, which is another form of time-of-flight spectrometer, when the molecule is ionized, the secondary electron which is split off is collected on an electron collector placed very close to the ion source. The positive ion passes in the opposite direction to an ion collector, a relatively much greater distance away. The difference in time between detection of the electron and detection of the ion is the time-of-flight of the ion, from which mass can be derived.

In each case, appropriate electronics and recorders provide a trace of the mass spectrum of the sample as a function of the mass number. Components of a sample can be identified by comparison of the spectra with known traces, or, for monitoring of specific components, corresponding mass peaks can be selected and used, for example, in breath by breath analysis to provide a continuous output proportional to the concentration of the specific components.

The mass spectrometer has a wide range of diagnostic versatility. In addition to its usefulness in monitoring toxic contamination of the cabin atmosphere, for which it might well be employed, and for other biochemical studies, it can be used as a fast response system for inhaled and exhaled oxygen, for exhaled carbon dioxide, and for nitrogen. All three gases, and for that matter,

helium, can be monitored from a single sample introduced via a capillary tube into the ionization chamber. Although all three types of devices are under 15 lbs. in weight further miniaturization and development is recognized before any could be incorporated into a space vehicle.

The gas chromatograph is another device which would have application to the analysis of respiratory gases. A prototype spaceborne gas chromatograph has been developed by Beckman Instruments, Inc., while other interested companies include Melpar Incorporated, and the Perkin Elmer Company. The principle depends on introducing a sample for analysis into a closed system containing an inactive carrier gas, normally helium, which carries the sample through pre-selected capillary columns containing either solid absorbents or liquid partitioning agents. The passage of the sample components is selectively retarded by the affinity of the components for the material in the columns. The components are separated according to their retention time. On elution from the end of the column they are passed to a sensitive detection system and identified. A common form of detector is a thermal conductivity cell. An ionization detector of the breakdown voltage type has been used. Several studies have been undertaken for the analysis of respiratory gases. Dressler et al. ( 83 ) used a Beckman system with a thermal conductivity cell detector for the analysis of oxygen and carbon dioxide with an accuracy of 0.1 volume per cent for the former and 0.8 for the latter, as compared to values obtained with a micro Scholander technique (.03 volume per cent).

Rapid response infrared carbon dioxide sensors have been devised, some of which are too large for consideration in spacecraft systems. Miniaturized carbon dioxide analyzers designed for atmospheric monitoring of spacecraft have been developed by Perkin Elmer and by Beckman. Their action depends on a highly specific absorption by carbon dioxide of light in the infrared band at  $4.28 \mu$ . The instrument is made selective by utilizing two filters, one transmitting the carbon dioxide absorption band and one an adjacent band. In the absence of carbon dioxide, the difference between the two transmissions, as measured on a detecting cell, is nulled out by a variable third filter. Introduction of carbon dioxide into the beam increases the

absorption in one filter. A signal is created proportional to the partial pressure of carbon dioxide in the sample. This type of atmospheric monitor does not appear to have been used for respiratory gas analyses but it could be modified for the purpose if required.

The nitrogen meter, marketed under the trade name of Nitralyzer by Med-Science Electronics, was originally developed by Lilly and his colleagues in 1943 , and has received wide acceptance and some modifications. The device is essentially an emission spectrograph. The sample is admitted into a partially evacuated sample chamber, electrically excited between the anode and cathode, and caused to emit radiation. The radiation discharge is filtered by passage through a filter specific for the wavelength emitted by ionized nitrogen, and thereafter detected by a photocell. The intensity is proportional, although not in a directly linear manner, to the content of nitrogen present. The meter is calibrated by samples of known nitrogen content. The current equipment is probably susceptible to further miniaturization and specialized development for space use.

Specialized oxygen meters have also been developed, notable among them being the paramagnetic oxygen analyzer originally developed by Pauling. Its action depends on the fact that oxygen intensifies a magnetic field and will increase the displacement of any diamagnetic material from the field. In this device nitrogen is contained within a glass dumbbell suspended on a quartz thread within an unsymmetrical magnetic field. In the presence of oxygen, the dumbbell rotates out of the field. The force required to return the dumbbell to a null balance point has a linear relationship to the  $pO_2$  of the sample and can provide a measure of the  $pO_2$ . The effectiveness of such a device or the weightless state, however, is open to conjecture.

The thermal conductivity meter (Cambridge Instrument Co., N. Y.) has a particular application to the measurement of helium, which, among the respiratory gases and contaminants, has an unusually high thermal conductivity. It has also been used for measurement of carbon dioxide, which has a distinctly lower thermal conductivity than oxygen. The instrument, although used previously for other forms of physico-chemical analysis, was first employed for respiratory gas analysis by McMichael ( 217 )

who utilized it for hydrogen analysis in determining lung volumes. It was Later used by Meneely and Kaltreider ( 223 ) for helium determinations. The method depends on creating an imbalance in two arms of a Wheatstone bridge exposed to the cooling effect of the sample, the other two arms being sealed. The imbalance is read on a galvanometer. Response time of the Cambridge instrument is relatively slow (20 secs to several minutes) and it is not suitable for breath by breath analysis. In Meneely's work the accuracy was comparable with that obtained by manometric techniques.

An acoustic gas analyser based on the changes that occur in the velocity of sound in different gases was described by Faulconer and Ridley ( 97 ) on the basis of work previously done in the Mayo Clinic. Quantification depends on measurement of the delay in transmission of pulses, or the phase shift of sound, in the ultrasonic frequencies. The instrument (National Instrument Laboratories) has a very high sensitivity (0.004% for oxygen and 0.0008% for carbon dioxide) but is complex and requires concentrated attention and skill in operation. It is doubtful if the extreme sensitivity is an overweening advantage for space use.

From the above discussion it is apparent that many methods are available, and feasible, for respiratory gas analysis in orbital space conditions, dependent on volume, skill, and experimental requirements. There is no doubt that the mass spectrometry is the most versatile technique, and also lends itself to other atmospheric and biochemical analysis. It is not intended here, however, to select any one technique or instrumentation system as being superior to another. A comprehensive trade-off study is required, taking into account all potential uses of such instrumentation, as related to the specific mission, specific vehicle, crew, size, available skills, etc., before any particular instrumentation system could be selected. In any event, the system, or systems, selected, will require further specific development related to the requirements for which they will be used and the craft and conditions in which they will be employed.

## ALVEOLAR GAS EXCHANGE

In consideration of methods for determining the adequacy of alveolar gas exchange in a space vehicle, it becomes increasingly necessary to bear in mind the reason for those measurements. The reason is not primarily to elucidate some of the more esoteric mechanisms in respiratory physiology, but to determine any changes, or trends towards change, that may occur by reason of, or in association with, exposure to an uncommon environment. This requirement should be met by the simplest clinical laboratory testing compatible with acquisition of the desired results. In some cases, even this may not be very feasible.

Satisfactory alveolar gas exchange depends upon adequate alveolar ventilation, uniformity of gas distribution and blood flow, and unimpaired gas diffusion.

### Alveolar Ventilation

Minute ventilation is the volume of air or gas entering the respiratory passages each minute. Alveolar minute ventilation is the volume of fresh air entering the alveoli each minute. Effective alveolar ventilation is the fraction of the total ventilation which comes in contact with well-perfused alveoli. The elements making up alveolar minute ventilation ( $\dot{V}_A$ ) are the tidal volume (TV), the anatomic dead space ( $V_D$ ) and the respiratory frequency (f). Thus:

$$\dot{V}_A = (TV - V_D) \times f \quad (22)$$

The anatomic dead space is the volume of the conducting airway which does not take part in gas exchange. Measurements of respiratory frequency and tidal volume have already been discussed. Measurements of the anatomic dead space in an oxygen-nitrogen environment is commonly made by the single breath oxygen technique of Fowler (104). In this procedure, expired nitrogen concentration is continuously recorded by a nitrogen meter, along with volume flow rate, after a single breath of pure oxygen. The expired nitrogen concentration remains effectively zero until the dead space volume has been expired, at which point it theoretically rises in a square

front to a plateau representative of alveolar nitrogen concentration. Because of mixing between dead space and alveolar space, a square front is not in fact formed, but by visual examination of the trace an equilibrium point can be determined indicating the position where a theoretical square front would lie. The dead space volume is the volume of air expired from the beginning of expiration to the time of occurrence of the theoretical square front.

It is apparent that this technique would not be feasible in a pure oxygen environment. With other mixed gas environments, such as oxygen-helium, or oxygen-neon, presumably the concentration of the diluent gas could be monitored similarly to provide the same information. Techniques with ambient gases other than air would require validation, however, before they could be recommended.

Instead of graphic analysis of the trace, the volume of the dead space can be derived from Bohr's equation, as follows, utilizing the symbology recommended by the American Physiological Society ( 248 ):

$$V_D = \frac{[FA_{N_2} - FE_{N_2}]}{[FA_{N_2} - FI_{N_2}]} VE \quad ( 23 )$$

At the end of the single oxygen breath,  $FI_{N_2}$  is zero, and the equation becomes:

$$V_D = \frac{[FA_{N_2} - FE_{N_2}]}{FA_{N_2}} VE \quad ( 24 )$$

$FA_{N_2}$  is obtained from the nitrogen meter;  $VE$  is obtained from an integrating pneumotachograph, while  $FE_{N_2}$  is obtained by dividing the area under the nitrogen curve for a given expiration by the duration of that expiration.

Dead space varies with age, sex, extent of lung distension, posture, disease, and the sequelae of surgical interference, but mean values are shown in the following table.

Table 7

ANATOMIC DEAD SPACE (ml)  
IN HEALTHY SUBJECTS  
(mean value)

Young women (semirecumbent)	104
Young men (semirecumbent)	156
Young men (supine)	115
Young men (during maximal expiration)	110
Young men (during maximal inspiration)	230
Older men (semirecumbent)	180

Source: Comroe ( 64 )

Commonly a mean value of 150 ml is used as a representative figure for young healthy men, although Radford (1964)<sup>88</sup> points out that the dead space volume of an adult in ml is approximated by his ideal weight in pounds.

Of more significance than the anatomic dead space is the physiological dead space, although in the normal healthy adult the two should be identical. The physiologic dead space includes the anatomic dead space and the portion of the alveolar ventilation, which, because of uneven relationships between pulmonary blood flow and functioning alveoli, is ineffective in arterializing venous blood.

The physiologic dead space can be calculated by applying Bohr's equation to measures of expired carbon dioxide, which is eliminated only where functioning alveoli are adequately supplied with pulmonary blood flow, thus:

$$V_D = \frac{[F_{A_{CO_2}} - F_{E_{CO_2}}] VE}{F_{A_{CO_2}}} \quad ( 25 )$$

- where
- $V_D$  = dead space volume
  - $F_{A_{CO_2}}$  = proportion of  $CO_2$  in alveoli
  - $F_{E_{CO_2}}$  = proportion of  $CO_2$  in expired air
  - VE = expired volume

Although the measure can be readily quantified by infrared sensor, glass electrode, mass spectrometer, or gas chromatograph, the fraction of alveolar  $CO_2$  is a difficult measure to obtain, since it is difficult to determine at what point in the respiratory cycle the measure should be made; but if there is no significant alveolar dead space ventilation or venous-to-arterial shunts the equation can be restated in terms of partial pressures, with the alveolar  $P_{CO_2}$  represented by the arterial  $P_{CO_2}$ , thus:

$$V_D = \frac{[P_{a_{CO_2}} - P_{E_{CO_2}}] VE}{P_{a_{CO_2}}} \quad ( 26 )$$

Use of this equation, however, requires a sample of arterial blood, and determination of the carbon dioxide tension within that sample. The taking of arterial samples under orbital conditions cannot of course be considered lightly. The problems of sampling and determination of gas tensions will be considered later.

Utilizing the same principle, namely, that expired carbon dioxide must be derived from mixed venous blood in association with functioning alveoli, the effective alveolar ventilation can be calculated directly from measurements of expired carbon dioxide.

Thus:

$$\dot{V}_{CO_2} = F_{A_{CO_2}} \dot{V}_A \quad (27)$$

rearranging,

$$\dot{V}_A = \frac{\dot{V}_{E_{CO_2}}}{F_{A_{CO_2}}} \quad (28)$$

Again, however, a representative alveolar sample is required and results may vary according to the type of sample. With appropriate conversions, and assuming normal ventilation/perfusion relationships, the carbon dioxide tension of arterial blood can be used instead of an alveolar measurement. Correcting for conversion, where required, from STPD to BTPS, and from fractional concentration to partial pressure, equation (7) becomes:

$$VA(ml) = \frac{\dot{V}_{E_{CO_2}}(ml) \times 0.863}{P_{a_{CO_2}}} \quad (29)$$

Summarizing the requirements for determination of alveolar ventilation in an orbiting spacecraft, it is apparent that dead space volume is the critically difficult measure. Under most circumstances in the normal healthy adult an assumed value can be used. For orbital space conditions, however, it will be necessary to establish first whether any change in dead space occurs as a result of weightlessness. Since dead space volume varies with posture, such a hypothesis would seem reasonable. The most feasible method to

obtain the measure in an oxygen - nitrogen environment would seem to be the single oxygen breath technique, using a nitrogen meter and integrating pneumotachograph. In a pure oxygen environment that technique would not apply, but physiological dead space could be estimated from carbon dioxide elimination measurements.

While results obtained utilizing arterial blood samples are considered to provide a more accurate representation of alveolar ventilation and dead space, the traumatization of the subject is not considered justifiable for the purpose. At the same time, consideration could be given to the use of capillary blood samples and estimation of  $P_{CO_2}$  by glass electrode techniques. This will be considered later.

If no change is found in dead space volume associated with orbital conditions, further space-borne measures of dead space would be unnecessary. Representative values from tables such as Table ( 7 ), or values obtained from pre-flight ground studies, could be employed and alveolar ventilation calculated from total ventilation and frequency.

#### Uniformity of Alveolar Ventilation

In a review of the intrapulmonary distribution of inspired gas, Fowler ( 106 ) cites the work of different authors to show that even in the normal healthy person gas is not evenly distributed to all alveoli. Some are hyper-ventilated and some are hypoventilated. In the orbiting space vehicle the picture might be still further modified by redistribution associated with loss of hydrostatic pressure head in the lung, or perhaps by patchy atelectasis associated with a high oxygen pressure.

Traditionally, clinicians have obtained a qualitative impression of ventilation distribution in the lungs by use of the stethoscope, and most certainly the trained ear can detect relative differences with remarkable sensitivity. In addition, with the use of standardized x-ray procedures, changes in relative radiolucency are also interpreted as representing

changes in ventilation distribution. However, while the skilled use of a stethoscope would be strongly recommended to provide an indication of ventilation distribution, it is doubtful if the foreseeable state of the art in space-borne radiography would justify a primary recommendation of the latter for that purpose. If radiological equipment is deemed advisable for other purposes, however, its use for standardized chest x-rays could provide useful corroboration of other findings.

Various forms of physiological testing have been used to determine the occurrence and extent of uneven gas distribution ( 26, 66, 70, 75, 180 ), in addition to consideration of radiological translucency, but certainly one of the simplest is the single oxygen breath test of Fowler ( 104 ) already described in connection with measurement of dead space volume.

The extension of this test is predicated on the fact that the "plateau" formed on the trace representing the alveolar nitrogen concentration is not in fact horizontal but, in the normal adult, after expiration of the first 750 ml, shows a slow increase in concentration up to 1.5% during expiration of the next 500 ml. Where unevenness of distribution on inspiration is more marked, and where rates of gas flow on expiration are unequal, it may show an increase in concentration up to as much as 16%. The test thus provides a semi-quantitative measure of ventilation distribution, in addition to an estimate of dead space.

Some other techniques are based on the washout of nitrogen which occurs when oxygen is breathed continuously for a specified duration. The simplest technique involves the breathing of oxygen for 7 minutes followed by a forced expiratory sample. With normally even distribution, nitrogen will be washed out evenly during the oxygen breathing, and the final sample will contain less than 2.5% nitrogen.

As a more complex alternative, nitrogen elimination can be continuously monitored, breath by breath, and a curve derived showing the exponential fall in nitrogen concentration ( 107 ). Plotting of the data on semi-log paper, along with a plot of the theoretical elimination rate, allows analysis of the data to provide a measure of slow and fast clearance.

When there is uneven ventilation, although the inequality may be distributed throughout the alveoli, the nitrogen clearance may be manifested as though there were a poorly ventilated portion with slow wash-out and a well ventilated portion with fast washout, each of which can be represented by a straight line on semi-log graph paper. The extent of the unevenness may be indicated by the amount of deviation of the actual values from a true line.

The techniques described require the presence of a two-gas atmosphere. In the presence of air, or oxygen-nitrogen, measures are made from a nitrogen analyzer. In oxygen-helium, or oxygen-neon, presumably the same principles would apply, but validation of the techniques would be required. The techniques of course would be inapplicable to an oxygen atmosphere.

In the latter case, if deemed advisable, and in fact in other atmospheres, as well, use could be made of the closed-circuit helium technique devised by Bates and Christie (26). In this technique, akin to that used in closed-circuit helium measurement of residual capacity, a known volume of foreign gas such as helium is added to a closed circuit system and its dilution by alveolar gas is monitored by, for example, a mass spectrometer. The resulting curve of concentration versus number of breaths provides an index of uniformity of distribution. As was noted in discussion of residual capacity measures, the necessary equipment is bulky and complex, and although the method would be applicable to pure oxygen atmospheres as well as oxygen-nitrogen atmospheres, a source of helium would be required. The method could not be used in an oxygen-helium atmosphere, although if necessary, nitrogen could be used for a tracer in this situation.

Thus, to determine the uniformity of ventilation distribution, it would seem that the stethoscope in skilled hands, and perhaps chest radiography, would provide useful qualitative information. More definitive, but relatively simple testing would involve the single breath oxygen technique with continuous monitoring of nitrogen (or the other diluent gas in two-gas atmosphere), to be carried out in conjunction with determination of dead space. There is no doubt that more complex techniques would provide still more

definitive information, but their added complexity under difficult circumstances makes their justification dubious. In a pure oxygen atmosphere the use of a closed circuit method with an added foreign gas would be mandatory, but again the complexity makes justification of the operation difficult.

### Uniformity of Capillary Blood Flow

Clinicians have realized since the 19th century, or before, that pulmonary capillary blood flow is not uniformly distributed, and that its distribution is probably affected by the gravitational vector ( 243, 339 ). As a result, flow under terrestrial conditions is greater in the lower lobes in the standing position. It would seem reasonable to hypothesize that this relationship will change under the weightless conditions of space. It most certainly becomes more marked under conditions of applied sustained acceleration ( 21, 347 ). In addition, distribution can be still further affected by pathology and disease.

As a result, various combinations of normal and abnormal alveolar gas distribution, and normal and abnormal pulmonary capillary blood flow, can arise. These in turn can produce various degrees of local hypoxemia, which result effectively in various degrees of venous-to-arterial shunt. The normal relationship in healthy man, the ventilation/perfusion ratio, is expressed as:

$$\frac{VA}{Q_c} = 0.8 \quad ( 30 )$$

Gross alterations in ventilation or perfusion will alter the ratio unless the individual alterations are such as to compensate for each other. Should the ventilation and perfusion of an alveolus, or group of alveoli, be such that mixed venous blood flows by unventilated alveoli, an absolute shunt will exist. The extent of this absolute shunt can be estimated by measuring arterial blood oxygen during the inhalation of oxygen. If the shunt is great enough, the arterial blood oxygen will not be increased, despite the inhalation of oxygen, since the latter does not gain access to the shunted blood. The question of arterial blood sampling will be considered later. It is

very doubtful, however, if the above procedure would provide information of value in orbital space conditions.

Acquisition of more definitive information on the extent of venous-arterial shunts, to include both absolute shunts and expressions of low ventilation/perfusion ratio, rightly belongs to the ground-based cardio-pulmonary laboratory, and could not be reasonably considered for routine use in an orbiting space laboratory. It is conceivable that a special experiment might be set up with specially trained experimenter and subject. The procedure depends on the fact that the amount of oxygen in arterial blood is made up of the oxygen in oxygenated blood plus the oxygen in partly, or fully, shunted blood.

Thus:

$$CaO_2 \dot{Q} = CcO_2 \dot{Q}_c + C\bar{v}O_2 \dot{Q}_s \quad (31)$$

where  $CaO_2$  = arterial oxygen concentration  
 $\dot{Q}$  = total blood flow  
 $CcO_2$  = pulmonary capillary oxygen concentration  
 $\dot{Q}_c$  = blood flow through capillaries  
 $C\bar{v}O_2$  = mixed venous oxygen concentration  
 $\dot{Q}_s$  = blood flow through shunt

Now  $\dot{Q}_c = \dot{Q} - \dot{Q}_s \quad (32)$

therefore  $CaO_2 \dot{Q} = CcO_2 (\dot{Q} - \dot{Q}_s) + C\bar{v}O_2 \dot{Q}_s \quad (33)$

rearranging  $\frac{\dot{Q}_s}{\dot{Q}} = \frac{CcO_2 - CaO_2}{CcO_2 - C\bar{v}O_2} \quad (34)$

Thus, the extent of the shunt can be measured in terms of the total pulmonary blood flow, or cardiac output. The technique, however, is too complex for consideration as a measurement within a space vehicle.

Still other methods of determining ventilation distribution and blood flow have involved the use of inspired radioactive materials and radioactive injectates. Hugh-Jones and his colleagues (79, 340) have used radioactive

oxygen-15 in studies of regional blood flow; Bates and his associates ( 20 ) have used radioactive xenon, both inspired as an insoluble material and injected, whence it is eliminated in the lung; and Markason and his colleagues ( 210 ) have used radioactive krypton for the purpose. The complexity of instrumentation and techniques render the procedures unacceptable, however, as well as the fact that the half-life of oxygen-15 is two minutes, that of krypton-85 is 4-1/2 days, and that of xenon-133 is 7-1/2 days.

While these procedures are not feasible for space use in the foreseeable future, useful qualitative information can be readily obtained from the single breath carbon dioxide expiration test ( 65 ). Since expired carbon dioxide comes from alveoli with a significant capillary blood flow, continuous rapid analysis of a single expiration by, for example, an infrared analyzer, will give qualitative information on ventilation perfusion relationships provided that ventilation is asynchronous i. e., if the early portion of the expired breath comes from well ventilated regions and the later portion from poorly ventilated regions. Disregarding again the first 750 ml of expiration, which may contain gas from the anatomic dead space, continuous rapid response analysis is made of the remainder. If the concentration of carbon dioxide is only slightly greater at the end of the analysis than the beginning (allowing for continued elimination of carbon dioxide) the V/Q ratio can be considered similar in both the poorly and well ventilated regions. If ventilation is uneven but matched by uneven perfusion, the concentration of carbon dioxide will be the same throughout expiration. If the last portion of analyzed gas shows a considerably higher concentration than the first, then the first part must come from a region with an increased ratio and the last portion from a region with decreased ratio.

Thus, while much investigation remains to be done in space as well as on the ground, the only potentially feasible method of investigating ventilation perfusion relationships at this time would seem to be the analysis of expired carbon dioxide, perhaps backed up by chest radiography.

## Diffusion Capacity

The diffusion capacity defines the ability of gases to pass between the alveoli and the hemoglobin through the alveolar-capillary membranes and the intervening materials. As with measures of ventilation-perfusion ratio, measurement of diffusion capacity cannot be considered routine in orbital space laboratories, and, except perhaps for a special experiment with special equipment, skilled investigator, and trained subject or subjects, it is probably not feasible in the foreseeable future.

Determination calls for a measure of the flow of gas across the tissues as related to the pressure differential dictating that flow. The measure, for accurate representation, requires the use of gases with an affinity for hemoglobin such that their diffusion capacity is not falsely influenced by varying capillary blood flow. The gases used are carbon monoxide and oxygen.

Several techniques have been described for the use of carbon monoxide in this manner since the original work of the Kroghs in 1910, and the techniques, although complex have been refined into various standard forms. It would be a pointless exercise to describe them in detail since any procedure selected for special orbital experiment would depend on the experimenter. A rebreathing technique has been described by Krouhoffer <sup>( 181 )</sup> using radio-tagged carbon monoxide; a steady-state breathing technique which requires a measure of arterial  $P_{CO_2}$  for the computation of alveolar carbon monoxide tension is described by Filley and his colleagues <sup>( 99 )</sup>; another steady-state technique entails calculation of alveolar  $P_{CO}$  from inspired and expired carbon monoxide concentrations, using an assumed dead space volume <sup>( 25 )</sup>; still another method requires inhalation of a single breath of low concentration carbon monoxide in helium, oxygen, and nitrogen, followed by breath holding and subsequent calculation of mean alveolar  $P_{CO}$  from Krogh's exponential equation describing take-up of alveolar carbon monoxide <sup>( 241 )</sup>.

Smith and Hamilton <sup>( 308 )</sup> described a carbon monoxide method using a gas chromatograph for measurement purposes, and neon as the inert gas added for the purpose of measuring the initial alveolar CO concentration. Although they collected their samples in balloon bags and then expelled them

into a tonometer over mercury, it is probable that more direct sampling systems could be designed. This same group <sup>( 151 )</sup> have also fashioned a slide-rule for application of the Krogh formula for  $D_{CO}$  which provides an accuracy well within clinical requirements, and allows completion of the calculations in one to two minutes.

It is emphasized, however, that in addition to the complexity of the equipment and techniques, and in some cases the requirement for arterial sampling, the procedures in all cases require the use of a toxic gas which will be released into the closed system of a spacecraft atmosphere and may also leak from storage. Consequently they cannot be lightly recommended.

The use of oxygen, on the other hand, is physiological and safe. Determination of diffusing capacity with oxygen, however, is grossly complicated by several factors. Firstly, pulmonary capillaries already contain a significant partial pressure of oxygen (the more so in a pure oxygen environment) which cannot be neglected in determining the driving pressure; secondly, the capillary  $P_{O_2}$  undergoes change along the course of the capillary; and thirdly, the extent of  $O_2$  oxygen dissociation from hemoglobin is not related to  $P_{O_2}$  in a linear fashion ( i. e., the oxygen dissociation curve is S-shaped). These factors dictate the necessity for a complex integration procedure and measurement of arterial and mixed venous  $P_{O_2}$  at a high (21%) and low (12 - 14%) level of oxygen breathing to determine mean capillary  $P_{O_2}$  and the extent of venous admixture. In addition, the procedure requires measures of oxygen consumption and calculation of  $PA_{O_2}$  from measures of inspired oxygen and expired carbon dioxide tension. The technique is detailed by Lilienthal et al <sup>( 192 )</sup>. Principles and procedures for diffusion estimations are also outlined in reviews by Comroe <sup>( 64 )</sup> and Comroe et al., <sup>( 65 )</sup>.

Thus, in reiteration, it is considered that measurement of diffusion capacity, although perhaps possible under special circumstances and after a specific examination, cannot be regarded as feasible for routine determination in an orbiting space laboratory in the foreseeable future.

## BLOOD GAS AND pH

The effectiveness of gas exchange in the respiratory system is reflected in the gas concentration and tension in the blood. Thus, it becomes necessary to consider techniques for the determination of the content and partial pressure of oxygen and carbon dioxide in mixed venous and arterial blood, both as confirmatory measures, and to assist in the determination of other respiratory parameters. In addition, since these values are in part determined by the hydrogen ion concentration, it is also necessary to consider measures of pH.

Mixed venous blood, representative of venous blood from all parts of the body, is accessible only in the right side of the heart, and since mixed venous sampling requires intracardiac catheterization it cannot be considered acceptable for use in a space laboratory, except under very special circumstances.

In several test procedures, however, it becomes of critical importance to obtain representative samples of arterial blood. Normally, these are obtained by the use of a heparinized arterial needle and cannula inserted into the brachial artery. Insertion of the needle and collection of samples is a skilled procedure which may cause considerable discomfort to the subject. Thus, while its use might be considered under special circumstances, using willing scientist astronauts as subjects, it could not reasonably be considered for routine use.

Attention, however, has been directed towards the use of "arterialized" capillary blood as a substitute for arterial blood. On the assumption that capillaries at the arterial end of the capillary bed will be at a higher pressure and consequently bleed more freely, and will be representative of arterial blood gas, studies have been undertaken on capillary blood from the preheated ear lobe. Several of these have shown an acceptable correlation between the values for capillary blood and those for arterial blood determinations of pH,  $P_{CO_2}$ ,  $CO_2$  content, and oxygen saturation ( 15, 16, 118, 190, 191, 304 ). As an alternative, blood from a hand vein after 10 minutes immersion at 45° C has been found to be a suitable substitute ( 298 ).

One of the major problems, and one that is perhaps insoluble in a high oxygen environment, is the collection of capillary samples under anaerobic conditions. Shock and Hastings ( 302 ) collected their samples under oil, but this technique was found to be unsatisfactory, since, among other reasons, the oil absorbs carbon dioxide.

Lilienthal and Riley ( 190 ) developed a method of collecting ear lobe blood in a small rubber cup attached to a tuberculin syringe under "virtual anaerobic conditions" which they showed were satisfactory for the purpose. Sanz ( 287 ) has made direct measurements of pH with a pH electrode on the ear. Astrup's group ( 15 ) have collected their samples in capillary tubes, containing a dried heparin fluoride mixture, which are then placed in a specially designed apparatus for the determination of pH and calculation of  $P_{CO_2}$ . The quantities of blood obtained by this last technique are extremely small ( about 25 $\mu$ l). To obtain larger quantities, suitable for the necessary determinations, it would seem that some technique akin to that of Lilienthal and Riley is required as described above. The collection in the weightless state, however, is complicated by the fact that although blood will flow from the capillaries because of capillary pressure, it will not fall into a collecting cup; also, as previously noted, in a high oxygen environment the capillary blood flowing from the ear will be exposed, at least for several seconds, to a high partial pressure of oxygen. It would seem useful to develop a vacuum device to fit on the ear lobe, by which capillary blood could be sucked into a collecting syringe without undue exposure to the atmosphere. With such a device, even under weightlessness and in a high oxygen environment, capillary blood could be readily obtained and used as a substitute for arterial blood.

For actual blood gas analysis, investigators have traditionally relied on manometric methods such as those of Van Slyke, whereby the pressure of gas evolved from a sample of blood is measured following the addition of reagents in a closed system, and the volume of gas responsible for that pressure is calculated with reference to the gas laws. In the case of oxygen, percent saturation is determined by measuring similarly the content of a fully saturated sample and calculating the percent saturation. The system, however, requires the manipulation of a mercury column to adjust the pressure and consequently is gravity dependent. The Roughton-Scholander bubble technique ( 289 )

is likewise unsuitable because of the unpredictable behavior of a bubble in the weightless state. Foster (personal communication) suggests, however, that although developmental difficulties may be great, it might be possible to modify the standard gravity-dependent chemical analytic methods, by, for example, substitution of centrifugal force, surface tension, or plastic films for parts of the apparatus, with lightweight, simple, reliable equipment designed to provide absolute values inherently superior to those obtained by more indirect means.

A measure of oxygen saturation can, however, be obtained by spectrophotometric techniques. The absorption of light by hemoglobin in a hemolysed sample of blood shows a relationship described by Beer's Law, which indicates that, with the incident light intensity constant, the oxygen saturation at a given concentration of hemoglobin is a logarithmic function of the intensity of light transmitted through the solution. The extinction coefficients of oxyhemoglobin and reduced hemoglobin are different, and the difference is exaggerated by measuring the optical density at two different wavelengths, one providing maximum difference and one zero difference.

Spectrophotometric methods for determination of blood oxygen saturation using the Beckman DU spectrophotometer have been described by Nahas ( 231 ), among others, and also by Holling et al., ( 158 ), who compared the technique with Haldane and Van Slyke methods and found that above 60% oxygen saturation there was no significant difference among the three methods. A micro method, with collection of capillary blood in glass capillary tubes has been described by Auckland ( 18 ). The blood is hemolysed by freezing, subsequently thawed, sucked into a capillary cuvette and its optical density measured by spectrophotometer at two wavelengths.

Oximetry can be regarded as a form of spectrophotometry for the specific purpose of determining oxygen saturation. Light may be either transmitted through the specimen or reflected from it. In reflection oximetry, non-hemolysed blood is used, and, in fact, the oximeter can be applied over the skin. The wavelength of light (generally between 650 and 700 ) is chosen so as to give a maximum difference between the extinction coefficients of oxyhemoglobin and reduced hemoglobin. While the techniques are most applicable to the direct sampling of blood flowing through a cuvette, close correlations can

be obtained with results derived from an oximeter applied to the heated ear lobe. The work of Wood in this field is well known <sup>( 345 )</sup> and the value and disadvantages of ear oximetry have been previously discussed in considering determination of cardiac output. A review of the techniques of oximetry is also made by Comroe and Wood <sup>( 67 )</sup>.

Although the content of blood gases cannot be readily determined by standard methods in space conditions, it is probable that either a gas chromatograph or a mass spectrometer, or both, will be available in the spacecraft for atmospheric monitoring purposes. To use these systems for measurement of content or tension, however, requires that the gases first be evolved into some form of tonometer or cuvette. The separation of liquid and gas phases under these circumstances might well provide problems. Suitable reagents for the purpose would be saponin, with potassium ferricyanide, along with lactic acid if elution of carbon dioxide is desired. Thereafter, gases could be introduced into either of the devices either automatically or as a manual sample. In the field of gas chromatography, several systems for blood gas determination have been described, such as those of Chambliss and Nouse <sup>( 57 )</sup>, Lukas and Ayers <sup>( 201 )</sup> Thomas <sup>( 325 )</sup>, and Wilson et al., <sup>( 344 )</sup>, but very much less information is available on the use of the mass spectrometer for blood gas work. In any event, for use in space, if it considered necessary, techniques and equipment would have to be developed compatible with the space borne systems.

In addition to mass spectrometry and gas chromatography, several special methods are available for the measurement of oxygen tension. These have primarily been used for monitoring oxygen in a gas mixture. Although some of those used for monitoring gas mixtures are unsuitable for biological fluids, the polarographic oxygen electrode has an application for measurement of oxygen tension in blood. The principle of its operation depends on the fact that an inert metal electrode (platinum, gold, silver, etc.) negatively charged to 0.4 to 0.7 volts in an electrolyte solution will give electrons to dissolved oxygen, reducing it to  $H_2O_2$  or  $OH$ . The current passing into the solution from the electrode is directly related to the availability of oxygen. Clark <sup>( 61 )</sup> modified the original device by a system in which a thin membrane between the sample and the cathode allowed only oxygen molecules to pass, and prevented contamination of the cathode and

electrolyte. The Beckman/Spinco model, which demonstrates refinements over the original Clark model has received wide acceptance. This electrode consists of a platinum wire cathode sealed in glass, with its tip exposed, and a silver/silver chloride anode. Cathode and anode are immersed in electrolyte which is sealed in by a thin membrane of polypropylene or Teflon. The latter permits faster reaction but is less stable in use. It is also sensitive to  $\text{CO}_2$ . 90% response time with the former is in the range of 3-7 seconds. A micro electrode is also available from Beckman/Spinco mounted in an 18-gauge arterial needle for intra-arterial use. The electrodes are temperature sensitive and measures have to be made in a water bath at body temperature of  $37^\circ \text{C}$ . Calibration is necessary before use to determine scaling. This is accomplished by exposing the electrode to 0% oxygen and 20% oxygen (atmospheric) in a diluent gas.

The original Clark electrode had a point diameter of about 2 mm. It was sensitive to pressure and also required that the fluid be stirred or agitated in some manner to avoid formation of a stagnant layer immediately surrounding the electrode. This problem has been overcome by using as the cathode a fine platinum wire of diameter 0.001 inch.

The Beckman/Spinco model is mounted in a stainless steel cuvette and fitted in a water bath with appropriate ports. Lucite is unsuitable as a mounting since it absorbs oxygen. It is used in conjunction with a signal processor and readout system, Beckman Model 160 Physiological Gas Analyzer. A minimum sample volume of 0.3 ml is required. Further developments of the Beckman electrode include a model with stability of calibration for at least 30 days. The original Clark electrode with stirring device in a cuvette and water bath is available from the Yellow Springs Instrument Company.

Electrode systems are also applicable to the measurement of hydrogen ion concentration in blood. The principle of measurement of pH by an electrode depends on the development of an electromotive force between one electrode and another reference electrode when both are immersed in a test solution and linked by a potassium salt solution bridge.

The original "hydrogen electrode", which was unstable and subject to chemical "poisoning", gave way to the glass electrodes developed by McInnes and his colleagues ( 215 ) which have undergone considerable refinement since. In this type of electrode a special glass (commercial 015 glass) is blown to form a small bulb which is connected to the end of a tube of ordinary glass. Within the tube, a silver/silver chloride electrode is sealed in a buffered KCl solution. Incorporated into the assembly is a reference electrode which consists of a calomel half-cell connected to the unknown solution by a KCl salt bridge. When dipped into a test solution the special glass electrode allows the passage of hydrogen ions only from the solution. An external circuit measures the change in potential between the outside and inside of the glass membrane. The glass electrode has a very high output impedance, and the amplifier for the potential difference requires a correspondingly high input impedance ( $10^{11}$  ohms). The resistance of the glass membrane is also very temperature sensitive, doubling for each  $7^{\circ}\text{C}$  decrease in temperature. Consequently, the system has to be operated at a closely controlled temperature, normally  $37^{\circ}\text{C}$ . Before use, the electrode is calibrated against a buffer solution of known pH.

A continuous flow of electrolyte is required at the electrolyte junction. While this can be gravity driven in terrestrial conditions, some other form of drive is required for weightless conditions. The Beckman Micro Blood pH electrode (Beckman Instruments) includes a pressurizing system for this purpose. It has been designed for spaceborne use, and includes a modular water bath and an expandable sample chamber which maintains a sampling chamber volume equal to the sample volume, thus eliminating bubbles.

Radiometer of Copenhagen market an ultramicro precision system based on the design of Sanz ( 287 ). In this system the glass electrode is a capillary tube surrounded by a buffer solution at constant pH in a water bath. The sample is sucked into the capillary tube, directly from the arterialized capillary. The tube and reference calomel electrode are then dipped into a KCl salt bridge solution and the potential difference is

read from an appropriate pH meter. The system, however, is somewhat fragile, and would not be too suitable for space use.

The system developed by Astrup's group ( 15 ) and marketed by Radiometer, is also based on the work of Sanz, but the design complexities have been ruggedized, partially automated, and formed into a convenient hand held device, which, with accessories, can be used for determining  $P_{CO_2}$  and standard bicarbonate as well as pH.

Severinghaus ( 297 ) and his group have developed a small pH meter consisting of an electrode and liquid junction. Blood is sucked into the capillary and passes the liquid junction in the course of its travel. Movement of the liquid in the current system is gravity dependent but could readily be pressurized by syringe or some similar device. It would seem to have considerable application to space use.

The carbon dioxide electrode, originally described by Stow ( 320 ) and developed by Severinghaus and Bradley ( 299 ) utilizes the principle of the pH electrode. A small volume of mildly buffered bicarbonate is held against the end of the glass pH electrode by a membrane of, for example, Teflon, held in place by a butyl "O"-ring. A spacer separates the membrane from the electrode. When the electrode is placed in a solution such as blood, the membrane serves to isolate the electrode from the sample and other sources of contamination, but allows the equilibration of carbon dioxide between the sample and the bicarbonate. Passage of  $CO_2$  is registered on the electrode as a direct logarithmic function of the  $P_{CO_2}$  of the sample. The system is calibrated before use against a known concentration of carbon dioxide. The reference electrode is 0.1 M KCl calomel, making a liquid junction with the glass electrode. The KEL-F reference electrode is superior to some of the earlier electrodes made of nylon.

The original electrode utilized a saturated cellophane spacer between the membrane and the glass electrode which caused a slow response time and some deviation from linearity at low carbon dioxide tensions. Better response was found with a separation made of fibers of glass wool, or powdered glass wool, to the extent that response time is better than with

no separation at all, indicating some catalytic action ( 296 ).

Various membranes have been used to contain the bicarbonate, including Teflon, silicone, natural rubber, polyethylene, and cellophane, but although other membranes, such as Silastic, may provide a faster response than Teflon, the speed is achieved at a sacrifice of durability. A 1 ml Teflon membrane at 37°C requires 1 minute to reach 95% of final CO<sub>2</sub> equilibrium. Faster response can be achieved by employing a more permeable membrane or reducing the thickness of the bicarbonate layer, but this reduces the operating life between re-charge cycles. If kept moist the operating life may be several months.

The carbon dioxide electrode determines the CO<sub>2</sub> tension of only the unassociated molecules of carbon dioxide. Consequently, it cannot be readily used for measuring CO<sub>2</sub> content.

Anderson et al., ( 15 ) have used the Astrup pH electrode for determination of P<sub>CO<sub>2</sub></sub> in capillary blood, using a special apparatus for equilibrating blood with carbon dioxide at known tension. They measure the pH of the unknown sample, equilibrate the sample with carbon dioxide at one, or two, known tensions and re-measure the pH, from which the original tension can be calculated.

Carbon dioxide electrodes are available from the National Welding Company, which has an electrode with a cuvette volume of 50μ liters, and incorporates a reference electrode within the thermostated portion. Another is manufactured by Instrumentation Laboratories of Boston, also with a 50μ liters cuvette. Severinghaus-type electrodes are also made by Instrumentation Associates, Inc., and Beckman.

Readout for electrodes is made by electrometer or pH meter with sensitivity such as to discriminate 60μ V or 0.001 pH units. Several instruments are available, specially designed to accept all three electrodes. Instrumentation Laboratories (Boston) sells two meters with plug-in adaptors for standard electrodes. In addition, it markets a very reliable system incorporating electrodes, controlled temperature water baths, readout meter, etc. Although this system has not been designed for space use it could be so adapted.

The Beckman/Spinco Model 160 Physiological Gas analyzer has been incorporated into a closed system with modular temperature controlled water baths, continuous flow sampling, non-gravity dependent liquid junction for the pH reference electrode, readout, and switchbox.

Medical Research Specialties, San Francisco, sells a water bath containing the Beckman macro-electrode, the National Welding CO<sub>2</sub> electrode, and a Radiometer capillary pH electrode suitable for continuous flow or spot sample measurement. The bath also contains a stainless steel cup for equilibrating solutions with known gas tensions. It is not a closed system, however, and would be impracticable in space use.

Epsco Medical Instruments Division incorporates a 12-foot tape readout system with the Yellow Springs Instrument Company thermostated water bath containing the original Clark electrode, a National Welding Company CO<sub>2</sub> electrode and a pH electrode. Again, however, this system has not been designed for space use.

Several other pH meters and recorders are available which have not however, been incorporated into gas analysis systems.

To summarize the requirements for blood oxygen, carbon dioxide, and pH measurement, it is reiterated that intracardiac and even intra-arterial sampling cannot be reasonably considered for space laboratory use. Thus, peripheral venous and "arterialized" capillary blood must be substituted. Techniques for sampling the latter in weightlessness and a high oxygen environment require development. For measurement of oxygen saturation ear oximetry would seem to provide a relatively simple and reasonably reliable system, unless a spectrophotometer is available for other purposes, in which case its use would provide greater accuracy.

A gas chromatograph or mass spectrometer, if available, could provide information on blood oxygen and carbon dioxide content, and by equilibrating samples in 100% O<sub>2</sub> and remeasuring, could provide a measure of saturation. Techniques for introducing gases from the blood into these devices under space conditions require further development.

For routine measurement of gas tensions and pH, the gas and pH

electrodes provide a favorable approach. It is far from clear which manufacturer provides the best electrode or the best system, or even whether an integrated modular system should be favored under individual components. A trade-off study examining experimental effectiveness and operational suitability would assist the comparison .

In summarizing the conclusions, with respect to respiratory measures, it is emphasized that the foregoing analysis is the result of a theoretical study. Any recommendations made are those that suggest themselves as being the most hopeful, but require comprehensive testing for feasibility and effectiveness within the simulated, or in some cases the actual, environment of an orbiting space laboratory. Recommendations are included in each section of the test, but it is appropriate to re-summarize them here.

For measurement of most lung volumes and capacities, the use of an integrating pneumotachograph with display on an X-Y plotter would seem to be the most feasible approach, with electrical impedance pneumography as a back-up, and for prolonged intermittent or continuous traces. The requirements for actual spirometry seems doubtful, but, if necessary, the Wedge spirometer with X-Y display would be suitable.

Measurement of residual volume and functional residual capacity presents considerable difficulty because of bulk and plumbing complexity of apparatus. If necessary, however, in an oxygen-nitrogen atmosphere, the measure could be achieved by the closed-circuit method of Christie ( 60 ), with suitable oxygen and nitrogen analyzers. In an oxygen-helium atmosphere analysis of helium would be necessary. There is also some possibility, as noted, of using electrical impedance methods to obtain an index of functional residual capacity which could be applied to a previous measure made on the ground.

For measures of the mechanics and dynamics of breathing, the integrating pneumotachograph is again valuable for determining volume and flow, using the flow-volume loop for determination of its various attributes, including timed volumes, mean maximal flow rates, specific flow rates, and peak flow rates. Determination of maximum breathing capacity provides some difficulty. Although special devices can be used

for the purpose, it is very doubtful if their use would be justified. Useful information on MBC (or MVV) can be obtained from the flow-volume loop, using the technique of Bartlett et al., ( 24 ) to calculate a predicted MVV which could be used in place of an actual measured MVV.

Determination of pressure-volume relationships (static and dynamic compliance) introduces another major problem, namely, the requirement to obtain a measure of intra-esophageal pressure. This requires passage of an intra-esophageal catheter, which, while offering little discomfort to the trained cooperative physiological subject, will no doubt discourage the uninitiated. It is considered, however, that on special occasions, with willing scientist-astronauts, the measure could be implemented without undue difficulty, using a miniaturized pressure transducer mounted on a catheter tip, and displaying pressure and related volume on an X-Y plot. The same measures can be used for determination of the work of breathing. Measurement of compliance of the lung-thoracic cage system does not seem feasible in the space environment.

The same difficulty on obtaining pressure measurement applies to the determination of pressure-flow relationships. However, if measures of intra-esophageal pressure are made for compliance studies, it would be appropriate to undertake pressure and flow studies during the same experiment, using the electronic subtraction method of Mead and Whittenberger ( 222 ), described in the text. Alternatively, although with less assurance or reliability, the technique of interrupting the airflow through a pneumotachograph ( 63, 234 ) could be employed to derive some indication of the extent of pulmonary non-elastic resistance. Pulmonary viscous resistance is not amenable to direct measurement, but can be derived by subtraction of airway resistance from total pulmonary resistance. The only method of obtaining airway resistance, however, is by whole-body plethysmography.

At this point, it seems advisable to put in a plea for a space-borne whole-body' plethysmograph. As noted in the text, such a device would serve many useful purposes in respiratory measurement, including the determination of lung volumes, airway resistance, and pulmonary capillary

blood flow. In addition, as will be shown in another section, it can be used for determining body volume. Because of the need to have an external rigid box, neither the space-suit nor a flexible bag-type device would be suitable. It is possible, however, that a portion of the spacecraft, normally used for other purposes, could be modified for use, when required, as a whole-body plethysmograph. In a large manned laboratory, which in all likelihood will contain an airlock, the latter would seem to offer possibilities for this purpose. It is not suggested that a whole-body plethysmograph be carried on all missions. It is possible, however, that a mission might be flown in which interest could be concentrated on the respiratory system, in which case a whole-body plethysmograph would be a valuable addition to the laboratory armamentaria. The recent development of Vorwald in electric field whole-body plethysmography might also be borne in mind.

For measurement of oxygen consumption, both as an index of work performed and for use in other calculations, the integrating pneumotachograph can again be employed, along with an oxygen pressure sensing device. Kissen and McGuire ( 172 ) have demonstrated the feasibility of this approach, although their instrumentation could undergo considerable development before being qualified for space use.

With respect to respiratory gas analysis, it is apparent that traditional methods employing the Scholander or Haldane apparatus are not feasible in the weightless state. Numerous other methods, including mass spectrometry, spectrophotometry, and gas chromatography are possible for general use, depending largely on their availability for other purposes, while in addition, specific systems are available for measurement of carbon dioxide, nitrogen, oxygen, and helium. While mass spectrometry is the most versatile technique, and could be employed for atmospheric and biochemical analysis in addition to respiratory gas analysis, it is not reasonable at this time to recommend any particular measurement system or systems, as being the most suitable for selection. All that can be said at this time is that methods of respiratory gas analysis can be readily developed for use in an orbiting space laboratory, and will be

required for such measures. A comprehensive trade-off study is needed, taking into account all potential uses of such instrumentation, with particular reference to the purpose and type of given missions, the type of vehicle and its environmental control system, the size of crew, their tasks and their available skills, before any particular instrumentation system could be selected. It is very probable, however, that at least some physiological instrument may duplicate, and act as back-up for, environmental control instrumentation. In addition, the system or systems, selected in most, if not all, cases will require further development for space qualification and integration into a space system.

Assuming suitable instrumentation, measurement of alveolar ventilation from respiratory gas depends upon accurate measurements of dead space volume. The most feasible technique to obtain this measure in a two gas atmosphere would seem to be the single oxygen breath technique, using an appropriate diluent gas measure, such as a nitrogen analyzer in the case of nitrogen, and an integrating pneumotachograph. To determine effective ventilation, which is physiologically more significant, or in a pure oxygen environment, the principle of equation ( 29 ) could be employed, by which effective alveolar ventilation is calculated from measures of expired carbon dioxide (from, for example, an infrared CO<sub>2</sub> meter ) and arterial P<sub>CO<sub>2</sub></sub>. The latter, as has been noted can be obtained by the use of a glass electrode on a capillary blood sample.

Several techniques are in use to determine the uniformity of distribution of alveolar ventilation. As noted in the text, however, the complexity of the more definitive techniques renders them unsuitable for orbital laboratory use. It is considered that the stethoscope, in skilled hands, perhaps backed up by chest radiography, would provide useful qualitative information. More definitive, but still relatively simple testing would involve examination of the trace of diluent gas concentration to determine the rate and magnitude of increase in concentration during expiration, as described in the text.

Measures to determine uniformity of capillary blood flow, ventilation perfusion ratios, and diffusion capacity, present formidable difficulties in the orbiting manned space laboratory. Although several potential techniques are discussed, it is concluded that unless the information is specifically sought on a special mission with a skilled investigator and trained subject, the experimentation required belongs in the ground-based cardiopulmonary laboratory. Some ancillary qualitative information on capillary blood flow, however, can be obtained by continuous analysis of carbon dioxide in expired air, using the technique of Comroe et al., (65), in which it is assumed that expired carbon dioxide comes from alveoli with a significant capillary blood flow and that the early portion of the breath comes from well ventilated regions and the later portions, from poorly ventilated. The assumption is considered valid if the ventilation is asynchronous as determined by the single breath oxygen test. Thus, a qualitative impression can be obtained, based on the concentration of carbon dioxide in different portions of the expired air.

There would, however, appear to be no feasible methods for routine determination of diffusion capacity. Methods involving carbon monoxide are considered unwise because of the danger of contamination, while those using oxygen require measures of arterial and mixed venous  $P_{O_2}$  as well as exposure to hypoxia. The measure of mixed venous  $P_{O_2}$ , which requires cardiac catheterization, is considered unwise under circumstances, while the technique and procedures in general are extremely complex.

Measurement of arterial oxygen, carbon dioxide, and pH raises problems of a different nature. Arterial puncture, while only mildly hazardous, is uncomfortable and not considered appropriate for routine use on astronauts. With trained willing subjects it would be a feasible procedure. For regular use, however, sampling of arterialized capillary blood is considered to be an effective and simpler substitute, although suitable sampling techniques will need to be developed, particularly for use in a high oxygen partial pressure atmosphere. The traditional methods of blood gas analysis are, of course, inapplicable in the weightless

state. For oxygen and carbon dioxide analysis numerous other methods are available. These include spectrophotometry, oximetry (for oxygen), mass spectrometry, gas chromatography, and the use of specially designed electrode samplers, some of which have been minizturized and developed into combined systems appropriate for space use. Electrodes for pH measurement are also available.

For measurement of oxygen saturation, ear oximetry would seem to be the simples and most reliable procedure, although its accuracy and reliability are not accepted by all. There is no doubt that spectrophotometry would provide still greater accuracy. For measurement of blood oxygen and carbon dioxide content, a gas chromatograph or mass spectrometer would seem to be the most useful, particularly if already available for other purposes. After suitable equilibration of samples with 100% oxygen, values could also be derived for oxygen saturation. Techniques would have to be developed, however, for introducing gases from the blood into these devices in the weightless state. For routine measurement of gas tension and pH, the gas and pH electrodes provides a favorable approach. As with respiratory gas analysis, however, it is far from clear which manufacturer provides the most suitable electrode or the most appropriate system. Again, a trade-off study is desirable, which would take into account the suitability, reliability, compatibility with other systems, and the versatility of the respective instrumentation systems, as well as the operational constraints of power, weight, and volume, and the requirements for integration into the total space system.

## SECTION 3

### ANTHROPOMETRY AND BODY COMPOSITION

Traditionally the weighing scale and the tape measure have been part of the armamentarium of the clinician. It has commonly been the clinical practice to record a body weight, frequently measured by an assistant, along with some critical lengths and circumferences, dependent on the circumstances. Thereafter, by way of a physical examination and the exercise of skill, experience, and a remarkable capacity for unconscious observation and correlation, it is customary to make a reasonable evaluation of the health status and physical fitness of the patient. The anthropometrist, or physical anthropologist, on the other hand, has relied much less on unconscious observation, but has taken great pains to make a multitude of comprehensive and accurate measurements of his subject - weights, lengths, diameters, circumferences, etc. The first approach is normally adequate for its purpose, and relies upon the art and judgment of the clinician for its success, but allows for little in the way of reproducibility of measure and scientific evaluation; the second approach is highly scientific, although not immediately useful to the clinician for determining man's response to his environment.

Consequently, to determine the nature and significance of man's anthropomorphic characteristics, and to evaluate the changes that occur in health, disease, and environmental stress, it has been necessary to consider new approaches which combine at a practical level some of the elements of both the clinical and the anthropometric techniques.

These considerations have given rise essentially to two systems of determining body composition and its dynamic changes; one of these might be termed the somatolytic concept <sup>( 45 )</sup>, or "anatomy without dissection", while the other might be termed the multiparameter or functional concept. In each case, however, as will be observed, there is some overlap, since the somatolytic approach involves functional entities, while the functional approach includes certain anatomically definable components. In addition certain ancillary techniques involving radiography, ultrasonics, and photography have made valuable contributions.

## MEASUREMENT TECHNIQUES

To determine the investigative requirements and the applicable techniques that might be employed within the confines of a manned space laboratory, it is necessary to examine the different approaches in turn.

### Somatolytic Concept

The term somatolytic was coined by Brozek (45) to refer to "anatomy without dissection" and relates to analysis of the living body in terms of certain anatomically definable components. The techniques involved utilize measures or calculations of body density (densitometry), body water compartments (hydrometry), or body dimensions (somatometry), and in addition may employ supplementary (or, in some cases, primary) measures involving radiography, ultrasonics, and photography.

### Densitometry

The practice of densitometry as a means of providing information on body composition depends on the assumption that the body has two components - a fatty component and a non-fatty component - which can be distinguished by reason of different densities.

Calculation of the masses of the two components depends upon the Archimedean principle which states that in a physical system comprising two components of known densities, the relationships are given by:

$$m_1 = \frac{1}{d} \times \frac{(d_1 \times d_2)}{d_2 - d_1} - \frac{d_1}{(d_2 - 1)} \quad (35)$$

where  $m_1$  = mass of first component as a fraction of total mass

$m_2$  = mass of second component similarly, and  $m_1 + m_2 = 1$

$d_1$  = density of first component

$d_2$  = density of second component

$d$  = total body density

Rathbun and Pace (265) initially used this principle to formulate an expression defining the fat content of guinea pigs. They measured the specific

gravity of guinea pigs along with the total quantity of ether extractable fat and its specific gravity. With this information, they calculated the specific gravity of the fat-free, eviscerated guinea pigs. Having validated the principle, they went on to develop an expression for the estimation of fat from the specific gravity of the human body, using an empirically determined density for human fat and an estimated density for the fat free body. The resulting equation is stated as:

$$\%F = 100 \times \frac{5.548 - 5.044}{\text{sp. gr.}} \quad ( 36 )$$

where  $\%F$  = fat as a percentage of total body weight.

The human body, however, is not a simple two-component system consisting of a readily separable fat component and a non-fat component. Behnke and his associates <sup>(32)</sup> consequently defined a system comprising a "lean body mass" to which variable quantities of fat would be considered additive. Normal humans were considered to have similar ratios of water, protein and mineral components within the lean body mass, but could differ in the proportions of fat added. The lean body mass, however, is not deemed to be fat free, but is considered to be made up of 72% water, 19% protein, 7% mineral, and 2% essential lipids, with a total density of 1.100 and a density of 0.930 for the added fat. Utilizing these density values, the fat fraction of the total body weight (f) is given by the equation:

$$f = \frac{5.135}{d} - 4.694 \quad ( 37 )$$

Keys and Brozek <sup>(168)</sup>, however, showed that constant relationships are not, in fact, found in all cases among the components of the non-fat portion of the body, and that in particular the water content varies with the fatness of the individual. In addition, they demonstrated that human adipose tissue contains a variable amount of water and cellular tissue in addition to fat. Consequently, they approached the problem of determining the mass of body components from another angle, and defined, on the basis of empirical calculation and experimental evidence, a standard "reference man" of stated composition against whom the findings in individuals could be compared.

The reference man is defined as a 25 year old individual whose actual weight is identical with the tabular standard (believed to be representative of the ideal). Density was computed as 1.064 and the fat content was established as being 15.3%. The adipose tissue obtained by gain in obesity was characterized by a fat content of 64%, with 14% of extracellular water and 22% cell residue (46).

An individual who differs from the reference body by a weight fraction of adipose tissue, A, is characterized by a mean body density, d, related to A by:

$$\frac{1}{d} = \frac{A}{d_o} + \frac{1-A}{d_1} \quad (38)$$

where  $d_o$  is the density of the reference body, and  $d_1$  that of the adipose tissue,

Rearranging terms

$$A = \frac{1}{d} \left( \frac{d_o d_1}{d_o - d_1} \right) - \frac{d_1}{d_o - d_1} \quad (39)$$

A, however, is not pure fat; therefore, the pure fat fraction is:

$$\Delta f = A f_1 \quad (40)$$

where  $f_1$  is the fat fraction of adipose tissue. The total proportion of fat in the individual is:

$$f = A f_1 + (1-A) f_o \quad (41)$$

By substitution into equation 41 of A from equation 39, and rearrangement,

$$f = \frac{d_o d_1}{d} \left( \frac{f_1 - f_o}{d_o - d_1} \right) - \left( \frac{d_1 f_1 - d_o f_o}{d_o - d_1} \right) \quad (42)$$

where  $f_o$  is the fat fraction of the reference body.

Previously noted values applicable to the reference body may be expressed fractionally as follows:

$$\begin{aligned} d_o &= 1.064 \\ f_o &= 0.153 \\ f_p &= 0.64 \end{aligned}$$

Inserting these values into equations (39) and (42):

$$A = \frac{8.696}{d} - 8.172 \quad (43)$$

and

$$f = \frac{4.235}{d} - 3.827 \quad (44)$$

Siri (306) has undertaken a statistical analysis of the uncertainty associated with the determination of body fat by this method, including errors of measurement involved, and the influence of biological variability. He has shown that the standard deviation in the value of fat weight estimated by the densitometric methods is  $\pm 4\%$  of body weight, a sizeable difference. He showed further that even allowing for no error in measuring density the uncertainty would still amount to  $3.8\%$  of body weight because of normal variability in body constituents. In particular, significant differences from the average in any of the gross constituents, namely, water, protein, and mineral, would introduce an indeterminate error in the fat estimate which would be most marked in the presence of abnormal hydration.

Since analysis by densitometric methods alone produces an unacceptably large error, one might consider the estimation of the body fat fraction from measures of the total body water, on the basis that the proportion of water in the fat-free body is approximately  $73\%$  (245), and that there is a high inverse correlation between total water and ether-extractable fat.

The fat fraction is given by the equation:

$$f = 1 - \frac{w}{w'} \quad (45)$$

where  $w$  is the proportion of total body water,  $w'$  is the proportion of water in the fat-free body, and  $f$  is the total fat fraction.

The validity of this equation is predicated on the assumption that the body constituents bear a constant relationship to each other, and that adipose tissue consists of fat and a constant proportion of water. This assumption, of course, is probably unrealistic even under normal circumstances and would certainly not be realistic in conditions of altered hydration, or deviations in other constituent relationships.

Accepting the assumption, however, a subject who differs from a reference lean body is presumed to differ only in possessing a proportion A of adipose tissue. The total water and fat in the normally hydrated person is then the sum of these components associated with the proportion A in adipose tissues, and that associated with the proportion (1 - A) of the body corresponding to the reference lean body.

Thus,

$$w = A w_1 + (1 - A) w_0 \quad (46)$$

where  $w_1$  = proportion of water in adipose tissue  
 $w_0$  = proportion of water in reference body  
 $w$  = proportion of total body water

and,  $f = A f_1 + (1 - A) f_0 \quad (47)$

where  $f_0$  = proportion of fat in reference body  
 $f_1$  = proportion of fat in adipose tissue, A

Combining equations, the general relation between total fat and water is:

$$f = \frac{w_0 - w}{w_0 - w_1} (f_1 - f_0) + f_0 \quad (48)$$

Siri<sup>(306)</sup> has undertaken a statistical analysis of the technical and biological uncertainties involved in this method of estimating the fat fraction and has shown it to be  $\pm 4.8\%$  body weight.

Because of these uncertainties, and because the calculations are invalidated, in particular, in the presence of abnormal hydration, Siri has developed an equation in which densitometric and water measurements are utilized as independent variables. Use of water as an independent variable allows for the effect of variation in water content.

Development of the equation depends on the following fundamental relationships, namely:

$$f + w + p + m = 1 \text{ (unit wt.)} \quad (49)$$

where  $f$  = fat fraction of total body weight  
 $w$  = water fraction of total body weight  
 $p$  = protein fraction of total body weight  
 $m$  = mineral fraction of total body weight

and also

$$\frac{1}{d} = \frac{f}{d_f} + \frac{w}{d_w} + \frac{p}{d_p} + \frac{m}{d_m} \quad (50)$$

where  $d$  = density of total body

$d_x$  = density of each of the four fractions

The equation also calls for an assumed constant relationship between mineral and protein, namely,  $m = \alpha p$ , which is unaffected by normal hydration. On the basis of empirical data,  $\alpha$  is considered to be 0.35, or 7% of the fat free body weight.

Siri (306) also introduces a substitution into equation (49), namely,  $s = p + m = p(1 + \alpha)$  and gives the combined density of protein and mineral  $d_s$  as:

$$d_s = \frac{(1 + \alpha) d_m d_p}{d_m + \alpha d_p} \quad (51)$$

Thus, from equations (49), (50), and (51),

$$f = \frac{d_f}{d_s - d_f} \left[ \frac{d_s}{d} - w \left( \frac{d_s - d_w}{d_w} \right) - 1 \right] \quad (52)$$

Assigning numerical values, the equation becomes:

$$f = \frac{2.118}{d} - 0.780w - 1.354 \quad (53)$$

Statistical analysis of uncertainty in this equation shows a potential error amounting to  $\pm 2\%$ , an error that is considerably less than that with other densitometric methods. This approach is widely accepted for the determination of fat content. Measurements of extracellular fluid can also be used in conjunction with body density for estimate of fat fraction, but again the error is in the region of 4%.

Techniques for determination of total body water will be discussed later. Determination of body density, however, is far from a simple process in conditions of manned space flight.

Density is the ratio of weight to volume, and, under terrestrial conditions, is commonly calculated from measurements of underwater weight. Application of the technique for measurements of body density, and descriptions of the procedures, have been reviewed by Buskirk (52). The measurement is

preferably accompanied by simultaneous measurement of lung volume and residual volume in the gastro-intestinal tract.

It is very obvious, however, that underwater weighing is quite impracticable, and, in fact, invalid in the weightless state. Consequently, some other approaches are required towards the measurement of body weight and body volume in an orbiting space vehicle.

### Body Weight

Body weight is probably the most fundamental of anthropometric measurements, not only as an index of body size, but as a datum point for the calculation of other body indices, and as a reference for comparison. Comparison of an individual's actual weight with some accepted standard weight is the most widely used criterion for leanness versus fatness. The degree of overweight or underweight may be expressed as a percentage deviation of the actual from the standard weight, or as relative weight, expressed as a percentage. The fact that the constituents of body weight, namely, lean body, fat, water, etc., may vary widely in their percentage contribution to the total constitutes the fundamental limitation to interpretation of body weight as an index of body composition.

The various methods of recording and presenting body weight are discussed by Keys and Brozek<sup>(168)</sup>. These include the standard weight tables developed as a result of the Medical Actuarial Mortality Investigation of 1912, on which most currently used tables are based, as well as the later tables published by the Metropolitan Life Insurance Company<sup>(224)</sup>, which present weights considered to be ideal for age, sex, and body build, i. e., associated with the most favorable mortality rate. More important is the actual weight at a given time for comparison with a baseline reference, and the extent of any change in weight that may occur in the course of a mission. In point of fact, for the selected crew of a manned space laboratory, the weight relative to an external standard is of little significance.

It is of course, paradoxical to speak of body weight in the weightless situation of orbiting space flight. Weight is the force exerted by an accelerating mass; in orbital flight the acceleration of gravity is nulled. What is required is a measure of mass which can be interpreted in terms of weight.

The required accuracy of the measure is open to some question. Precision in the region of 20 gm has been discussed <sup>(288)</sup>, which for an 80 kg man would represent an accuracy of 0.04%. A change of more than this magnitude could be accomplished by voiding 1 oz of urine; consequently this degree of precision seems more rigid than necessary. The standard laboratory beam balance used for human weight measurement has an accuracy of  $\pm 1/4 - 1/2$  lb. Since scales with this degree of accuracy have been successfully used without adverse comment for ground-based studies, it would seem that an accuracy of this degree would be acceptable.

Design of an actual device to accomplish mass measurement in weightless conditions raises problems of considerable complexity. It is obvious that devices relying on the gravitational vector, such as spring scales and standard beam balance, are invalid, and it is necessary to investigate other physical properties. The most definitive work in this area, leading to the construction of working systems, has been done by Lockheed Missiles and Space Company in connection with the Biolabs study. Their presentation (81) defines the problems and the approaches that can be made towards solution, and is widely paraphrased in the ensuing paragraphs. The types of measure that have been considered include the torsion pendulum, the centrifuge, devices using the principles of impulse momentum, conservation of momentum, linear acceleration, resonant frequency of a spring-mass system, and a modified beam balance.

Torsion pendulum: The natural frequency of a torsion pendulum is given by:

$$f = \frac{1}{2\pi} \sqrt{\frac{\tau}{I}} \quad (54)$$

where f = frequency

$\tau$  = restoring torque/angular displacement

I is proportional to the product of the mass and the square of the radius

Since small changes in the location of the mass center would be reflected in the second power, appreciable errors would be observed unless the radius were very large. An appropriate radius would be larger than the available space within the vehicle.

Impulse momentum: The equation governing impulse momentum is given by:

$$F(\Delta T) = M(\Delta V) \quad (55)$$

where  $F$  = a constant or known force

$\Delta T$  = time period over which  $F$  is applied

$M$  = mass accelerated

$\Delta V$  = velocity increment

In other words,  $F(\Delta T)$  is an impulse which changes momentum  $M(\Delta V)$ . Since each is in effect for a very short time, both  $F$  and  $\Delta T$  would be very difficult to estimate with accuracy. Accuracy would be still further diminished by the presence of random acceleration forces. In addition, since man is a complex of different spring-mass systems he would not respond to the impulse as a unitary mass, and his response would be still further distorted by the nature of the system coupling him to the device.

Conservation of momentum: The principles employed in a system utilizing conservation of momentum in its design are given by:

$$MV_1 + mv_1 = MV_2 + mv_2 \quad (56)$$

In this system, a smaller known mass ( $m$ ) travelling with velocity ( $v_1$ ) impacts the unknown mass ( $M$ ) which has an initial velocity  $V = 0$ . The two masses are united on impact and  $V_2 = v_2$ . At this point the equation becomes:

$$M = (m/v_2)(v_1 - v_2) \quad (57)$$

and the only other unknown besides  $M$  is  $v_2$ , which is measured. To implement such a system however, would require an appreciable impact by a "small" mass of considerable size, which in itself would no doubt be unacceptable. In addition, the same reservations apply with respect to the varying mechanical impedances of man as a complex of spring-mass systems, as applied to the impulse momentum approach.

Linear acceleration: This method is represented by Newton's familiar equation:

$$F = Ma \quad (58)$$

where  $F$  = known constant force

$M$  = unknown mass

$a$  = measurable acceleration

Acceleration can be measured directly using a sensitive accelerometer, or indirectly by measuring the time,  $t$ , to traverse a known distance,  $s$ , on the basis of the equation  $a = 2s/t^2$ . Since time enters the equation in the second power, very careful estimation is required. Random accelerative forces can interfere with the accuracy of the results but the effect of coupling and differential mechanical impedances in the subject would be minimized because of the low rate of onset of acceleration, longer duration, and low peak.

Spring-mass system: The natural frequency of an oscillating spring-mass system is given by:

$$f = \frac{1}{2\pi} \sqrt{2K/M} \quad (59)$$

where  $f$  = frequency (cps)

$K$  = known spring constant

$M$  = unknown mass

In this system the mass is close-coupled to a platform mounted on a spring in a one-degree-of-freedom system. The mass is set oscillating in simple harmonic motion and the system frequency measured. Timing can be done with great accuracy by averaging over a number of cycles. Random accelerative forces, unless of considerable magnitude, will have little or no effect on the accuracy. Errors arising from coupling or differential response of body spring-mass systems will be minimal if the acceleration (proportional to  $f^2$ ) and jolt (proportional to  $f^3$ ) are kept low, and the body is held rigid.

Inertial beam balance: The traditional parallel platform beam balance such as is used in a commercial weight scale could be utilized in the weightless state if during weighing an accelerative force were applied at the normal balance point, on a vector perpendicular to the knife edge. The resulting inertial force that would be developed would substitute for the gravitational acceleration normally utilized in the weighing function. Random accelerative forces would reduce the accuracy, and a prolonged stroke would be necessary to overcome any problems associated with bedding down. Balance would be determined during the latter part of the stroke.

Centrifuge: The equation governing centrifugal force is:

$$F = M\omega^2R \quad (60)$$

where F = force

M = mass

$\omega$  = angular velocity

R = radius of path of mass center

In this system, which of course requires a manned centrifuge, random accelerative forces and differential impedances present no problem. Difficulty is encountered, however, in determining and consistently locating the mass center for measurement of the radius, and care is required in measuring angular velocity, since it enters the equation in the second power.

Of the measures examined, it is apparent that three show potential, namely, the use of a spring-mass system, a linear acceleration system, and a centrifuge. A fourth system, namely, the modified inertial beam balance, may well have potential, but without adequate simulation of weightlessness, or actual operational trial, its validity cannot be verified.

In connection with the Biolabs study, Lockheed undertook verification of the spring-mass system and the linear acceleration system. To minimize the contribution of the gravitational vector in the spring-mass system they used a horizontally oscillating platform constrained by springs fore and aft. The fundamental equation was modified to account for the pendulum effect of the support, and also the damping. Timing with a stop watch over a period of 40 cycles, with the subject rigid, and an acceleration of about

10 ft/sec<sup>2</sup>, produced repeatability within 0.4 secs, which represents variation in subject weight of  $\pm 1.5$  lb, or a percentage of error of more than 1% in a normal adult male.

Further development of the technique is described by Hall and his associates ( 144 ), with a seat mounted on wheels and a timing device for timing four oscillations. After calibration of the device, "several hundred" subjects, from 100 to 250 lbs., were weighed with an error that did not exceed  $\pm 1/2$  lb or a percentage error of less than 0.5%. Objects weighing from 3 to 20 lbs. were weighed with an accuracy of  $\pm 1/4$  lb. It might be noted that in weightless conditions the force components will be different and a new calibration will be required. A device working on the same principle has also been developed by astronaut W. E. Thornton for the weighing of small objects ( H. T. E. Hertzberg, personal communication).

A linear acceleration device was also validated experimentally ( 81 ). Subjects were seated on a wooden cart with minimal friction ball-bearing wheels. The cart was moved horizontally on a level surface to minimize the gravitational vector. Constant force was applied by a negator spring. For timing, a 1 kc oscillator was used as a reference source with an electronic counter connected into the circuit. Counting was initiated at the beginning of motion and stopped at the end of the measured distance. The total force includes various forms of drag, namely, ball-bearing friction, track friction, and inertial drag of the wheels, which act against the spring force. In orbital conditions, however, the force components would be different. With allowance for these factors, the fundamental equation can be rewritten in terms of weight, time, and distance. Measurement of the time to traverse the known distance permits calculation of a value for weight.

With eight subjects, ranging in weight from approximately 130 to approximately 200 lbs., all values except one fell within  $\pm 6$  lbs. of actual weight, that is, with an error of 3 - 4%. The exception may have resulted from overstressing of the equipment.

Because of the difficulties of determining the actual radius from center of rotation to center of mass, the acceleration research group at Douglas Aircraft Missile and Space Systems Division ( 342 ), developed a technique for measuring acceleration and force at two different radii which could be precisely measured by location of the supporting couch.

The theory is based on the following:

$$F_1 = M\omega_1^2 R \quad (61)$$

where  $F_1$  = force recorded at radius  $R$  and angular velocity  $\omega_1$

$$F_2 = M\omega_2^2 (R + \Delta R) \quad (62)$$

where  $F_2$  = force recorded at radius  $(R + \Delta R)$  and angular velocity  $\omega_2$

$$R = \frac{F_1}{M\omega_1^2} \quad (63)$$

Substituting in equation ( 28 ),

$$F_2 = M\omega_2^2 \left( \frac{F_1}{M\omega_1^2} + \Delta R \right) \quad (64)$$

$$= F_1 \left( \frac{\omega_2}{\omega_1} \right)^2 + M\omega_2^2 \Delta R \quad (65)$$

$$M = \frac{F_2 - F_1 \left( \frac{\omega_2}{\omega_1} \right)^2}{\omega_2^2 \Delta R} \quad (66)$$

Since  $M = W/g$

$$\text{then, } W = gF \frac{1 - \left( \frac{\omega_2}{\omega_1} \right)^2}{\omega_2^2 \Delta R} \quad (67)$$

Error analysis of the method, allowing for error in centrifugal force measurement and error in angular velocity measurement, showed a potential total weight estimation error of  $\pm 1.041\%$ . This error, however, is considerably more than the  $\frac{1}{2}$  lb. in 160 lbs which was deemed desirable.

The technique was validated experimentally using a chair mounted on rollers on the centrifuge in such a manner that it could be located radially along the centrifuge at each of two precisely fixed locations. The force applied to the chair and its load was presented on a strain gauge display at the mount, which could be read via a television camera. Angular velocity was determined electronically. The rpm required to maintain a pre-determined force at the strain gauge (400 lb) was measured by rotating the centrifuge with the load in position, at an angular velocity sufficient to

maintain the strain gauge display in the nulled position as determined by the preset force. This was done for each of the two radii. The resulting weight evaluation was found to have an error of about 1 lb in 180 lbs., which is greater than desirable. It is probable, however, that the system could be improved.

Employing a completely different principle, Kirton and his associates <sup>(171)</sup> in New Zealand evaluated the carcass weight of lambs as a function of capacitance. The capacitance meter consisted essentially of two parallel steel plates each 3 feet square, mounted on plastic backing and set 12 inches apart. The capacitance was read by way of a radio-frequency bridge operating at 5 millicycles. A background reading was made before and after insertion of each lamb, and the mean subtracted from the measure of each lamb. Actual weights and regression equations are not reported, and so it is not possible to determine the extent of the error, but a correlation of 0.895 was found, with a residual standard deviation of 3.77, between the measured capacitance and the live weight. Readings were affected by position of the animal in the meter and several problems were noted in execution. The technique, however, has possibilities and might well be worth further investigation.

It would therefore seem that there are several approaches towards estimating body mass in the weightless state in terms that can be interpreted as weight. It is difficult to recommend one very strongly over another. Most development work has been done on the spring-mass system with very promising results, but a centrifuge, if present for other purposes, will lend itself well to mass evaluation. It is possible that the accuracy currently achieved with the centrifuge can be improved upon, as can that using linear acceleration. The modified beam balance using an inertial force to substitute for gravitational force also has theoretical possibilities but cannot be validated except operationally. Development might well be encouraged in all four areas until hardware can be finally tested operationally.

### Body Volume

Assuming from the foregoing that a suitable method will be available for reasonably accurate measurement of body weight, a comparable measure of

body volume is also required for the calculation of body density. Actual measurement of body volume in orbital conditions would call for complex procedures. Consideration therefore has to be given to other methods of obtaining the data. Unfortunately the irregular shape of the body does not lend itself to simple calculations. Numerous empirical equations, however, have been developed relating body volume, surface area, weight, and height (6, 33, 244). From the data of Osserman et al., (244) on 78 young normal males, Sendroy and Cecchini (293) developed an equation which they found to be the most valid:

$$V = S(51.44 W/H + 15.3) \quad (68)$$

where V = volume in liters

S = surface area in square meters (calculated from photography)

W = weight in kilograms

H = height in centimeters

Using this basic relationship, Sendroy and Collison (294) collected data from many sources covering a very much wider range of body size, age, and sex in 737 subjects, and submitted the data to computer analysis to determine the relationships of V/S to W/H. Several different equations were derived, depending on subject type. From the data, they prepared diagrams showing the relationship of isovolume values to weight and height, and also to surface area. A diagram of this nature applicable to estimation of the body volume of males on the basis of height and weight is illustrated in figure (16).

Test of the diagram against values of body volume derived from numerous authors cited in Sendroy's report indicates that for the estimation of body volume of subjects varying from 19 to 126 liters, 95% of the results calculated by means of the diagram would be within 3.5% of the "true" value measured by other means.

The use of photography also has possibilities as a means of estimating body volume. In particular, stereophotogrammetry has been suggested as a useful tool (254) whereby two overlapping photographs of the same subject are made and viewed through a suitable stereoscope. Subsequent processing

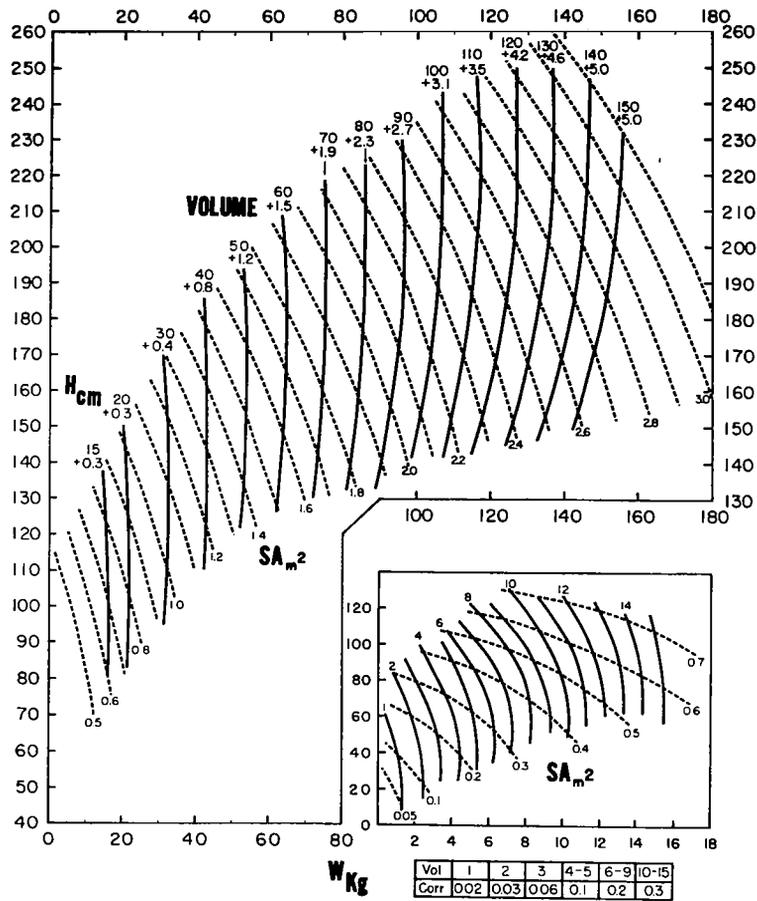


Figure 16. Diagram for the calculation of human body volume from measurements of height and weight. Values for V (solid lines) are for male subjects, with a correction shown to be added for females. (Insert is used for low range of infants from birth to attainment of volume of about 7 liters). This diagram may also be used for the estimation of body surface area (dashed lines) as developed by Sendroy and Cecchini.

After Sendroy and Collison (294).  
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leads to preparation of a contour map whereon points of equal height above an arbitrarily established datum line are joined in a contour line. With appropriate mathematical treatment, volume can be calculated from the contour lines. However, Pierson, one of the chief proponents of the method, points out that the mathematics and photography are complex, the plotting of contours requires great skill and costly apparatus, and the equipment is not readily portable. Consequently, the applicability of the technique to space conditions is dubious.

Hertzberg, however, who had done much work in this field maintains that extraction of data is nowhere so onerous as may be thought. Using telemetry, and commercial techniques of stereophotogrammetry involving automatic or nearly automatic methods, contour maps can be prepared from which data can be extracted in digital form ( 155 ). He also comments on the possibilities (personal communication) of using a suitably controlled laser beam to produce high-speed automatic contouring. The possibilities of developing the latter in suitable form, however, seem unlikely at this time.

Pierson ( 255, 256 ) has also developed an ingenious monogrammetric technique using color photography. The body is positioned vertically between two screens, each of which is made up of a series of vertical colored acetate strips of equal width through which a light is shone from each side. The body is photographed from front and back and the resulting print presents a color contour map. The volume is determined by a formula derived from surveying and mapping techniques, namely,

$$V = (a + 2b, 2c + \dots + 2n)/2 \text{ (contour interval)} \quad ( 69 )$$

where  $a$  is the area encompassed by the zero contour line (datum plane) and the contour interval is the width of the transparent strips. When compared with water displacement methods, the technique showed an error of less than 2%.

However, as currently used, the method calls for a camera-to-subject distance of 10 feet with a 21 mm lens to avoid distortion, while the light sources have been as much as 30 feet on each side. Consequently without further development the technique as expounded by Pierson is currently inapplicable to space laboratory use.

Direct or indirect measurement of body volume has been undertaken by water displacement, and special devices have been built for the purpose ( 122 ). Again, however, it is apparent that water displacement methods are impracticable in space conditions. Air displacement systems have been examined without much success by several groups. Some of the techniques are reviewed by Lim ( 196 ).

Essentially the air displacement methods depend on applications of the gas laws, whereby a known amount of air (or gas) is transferred into a rigid chamber of known volume containing the body of unknown volume. With measurement of chamber pressures before and after air transfer, the volume of the unknown body can be calculated. The simplicity of the technique, however, is complicated by the development of thermodynamic heat, by the presence of respiratory water vapor, and the effect of the respiratory gas exchange, all of which require complex compensatory regulation. Respiratory changes and changes in temperature can be compensated for by appropriate equations. Instead of adding air, the same principle can be invoked by suddenly reducing the pressure through a known amount. This technique has been used in measuring body volume of babies ( 96 ) and also of adults ( 156 ). The reduction in pressure, with consequent reduction in temperature, serves to some extent to counteract the temperature rise associated with the presence of a subject on the chamber. The other respiratory complications, however, are unchanged. Problems in this area have been examined in connection with development of the whole-body plethysmograph (See Respiratory System). Body volume per se would not appear to have been measured in the whole-body plethysmograph ( 84 ), but if, as suggested in the Respiratory Section, a whole-body plethysmograph were available for respiratory studies it could be modified for the purpose. Development under terrestrial conditions would be required to determine the nature of the modifications, the techniques to be employed, and the accuracy of the measure. Density estimations in dogs, using an air displacement method of the type described, have agreed within 1% of those determined on the same animals post mortem ( 196 ), even without making allowances for thermodynamic effects and respiratory gas exchange.

Another approach to measurement of body volume lies in the utilization of gas dilution principles, whereby an inert gas, soluble in body tissues, is used to provide an indirect determination of the solvent volume ( i. e., body tissues). In the method of Siri ( 305 ), helium is used as the solute gas. With a subject in a rigid closed chamber, the total volume of air, including air in the respiratory spaces, is  $V - V_s$ , where  $V$  is the chamber volume and  $V_s$  the tissue volume of the subject. If helium at atmospheric pressure, from a chamber of volume  $v$  is then mixed with air in the first chamber without altering the pressure or total volume of the system,

the concentration of helium and volume of the subject after equilibration are related by:

$$C_s = \frac{v}{(V - V_s) d_s + v} \quad (70)$$

where  $C_s$  = concentration of helium in tissue

$d_s$  = ratio of absolute temp ( $^{\circ}$ K) of helium and chamber air immediately before mixing

Continuous equilibration with atmospheric pressure in the chamber is ensured by allowing a small leak (equivalent to a 3 to 5 mm orifice in a 400 liter chamber).

To calibrate the chamber and derive a value for  $C_s$ , two independent measures are made in the chamber on known volumes which bracket the expected volume. While Siri uses Pyrex carboys for the purpose, it would be more practicable in an operational space situation to use collapsible plastic bags of 20 to 50 liter volume. Measures with reference volumes  $V_1$  and  $V_2$ , differing by 25 to 50 liters, produce responses in the helium detector system  $R_1$  and  $R_2$  and corresponding concentrations  $C_1$  and  $C_2$ . From these data and the detector response,  $R_s$ , from the subject, the helium concentration from the subject measure is given by:

$$C_s = \frac{C_1 + (R_s - R_1)(C_2 - C_1)}{R_2 - R_1} \quad (71)$$

From the value so obtained for  $C_s$ , and measures of gas temperatures, it is possible to solve for  $v$  in equation (70). Full details of the procedures are given in Siri's paper. The device, including the chamber, the blowers, the helium injection system, and the helium detection system, is complex, and regulation is critical. Permissible standard deviations are shown in the following table:

Chamber volume	$\pm 50$ cc
Helium volume	$\pm 1$ cc
Chamber temp	$\pm 0.03^{\circ}$ C
Helium temp	$\pm 0.02^{\circ}$ C

Overall error's in the hands of Siri amount to  $\pm 0.1$  liter. Various modifications of Siri's system have been made, one of the most useful, by Stern<sup>(316)</sup> in Sweden, incorporating an automatic heat control system.

In the original design, helium was detected by a thermal conductivity cell, but other methods of helium detection such as mass spectrometry could be used.

Hix and his colleagues <sup>(156)</sup> conducted a measured comparison of the helium dilution and air displacement systems of determining body volume, using a method akin to that of Siri for helium dilution, and a pressure reduction system of air displacement. In 24 men a highly significant correlation (0.99) was obtained in body volume measurements, with the helium dilution system producing consistently slightly higher values. A similar correlation was found in 24 women with no consistent change attributable to the measuring system.

From the point of view of use in space, there are grave disadvantages to both methods, including the volume and weight limitations, the complexity of the systems, and the requirement for a source of helium. However, there is no doubt that if it were deemed advisable, a certain area of a large laboratory, such as the airlock, could be modified for the purpose.

Regardless of whether air displacement or helium dilution is used as a measurement technique, some form of complex device will be required. The question arises as to whether the accuracy justifies the increased complexity over what is obtainable by calculation from weight and height or perhaps by photogrammetry. Siri <sup>(306)</sup> has indicated that for accuracy in densitometric measurements an overall error of  $\pm 0.1$  liter is the maximum tolerable. It is apparent that neither Sendroy's calculations nor photogrammetry can meet this rigorous requirement. Thus, while reasonable approximations for monitoring purposes might well be obtained by either of the last named systems it would seem that for accurate data a more complex system would be required, incorporating some form of chamber. In view of the added complexity incurred by the requirement for a helium source it would seem that an air (or pressure) displacement system would be the more appropriate, utilizing the modified whole-body plethysmograph previously suggested.

## Somatometry

The term somatometry is applied to the system of anthropometric measurements that can be made upon body dimensions, and includes the various lengths, widths, circumferences, and diameters of the body and its members, as well as the thicknesses of fat or skin folds at sundry sites, and body weight, which has been previously considered.

To describe the body form, it is apparent that weight and stature (or height) are fundamental parameters. It is equally apparent that weight and height are only loosely related, although various equations have been developed, with somewhat poor correlations, linking one with the other. On the assumption that in the mature adult the body comprises a lean muscular fraction, a skeletal fraction and a fat fraction, and that the major temporal variation is related to a variation in fat content, measures are required to provide indices of the muscular skeletal portion and the fat portion. While this approach makes little or no direct allowance for changes arising from alteration in the content and distribution of body fluids, or compositional changes in body tissues, it has led, on a semi-empirical basis, to the making of various measurements among which significant relationships are found, and to the development of numerous regression equations showing high correlations.

Thus, to refine the standard height-weight measure with a measure of laterality, the Committee on Nutritional Anthropometry <sup>(232)</sup> recommended the addition of a measure of the bi-iliac and bi-acromial diameters.

The bi-iliac (bicristal) diameter is obtained as the greatest distance between the lateral margins of the iliac crests, while the bi-acromial diameter is defined as the distance between the most lateral margins of the acromial processes of the scapulae. Along with stature, these measures provide an indication of skeletal development. To incorporate an index of muscular development is more difficult, particularly in men, since the extent of local development may be influenced by the nature of the occupation. Brozek <sup>(42)</sup> used the upper arm diameter, corrected for subcutaneous fat, in the following equation:

$$Y = 0.411X_1 + 1.204X_2 + 0.885X_3 + 7.342X_4 + 0.220X_5 - 135.510 \quad (72)$$

where Y = predicted body weight (Kg)

$X_1$  = height (cm)

$X_2$  = bicristal diameter (cm)

$X_3$  = bi-acromial diameter (cm)

$X_4$  = corrected upper arm diameter (cm)

$X_5$  = age (yrs.)

Deviations from standard weight were considered to represent largely the amounts of adipose tissue by which an individual differs from the "average" man.

Behnke and his colleagues employed another approach, which increased the number of measurements, but introduced a greater simplicity of measure, since all could be made with a simple linen tape (29, 30, 31). On the assumption that the body could be considered as a kind of cylinder, a relationship between weight (w) and height (h) can be written as  $W = \pi R^2 h$ , or  $R = \sqrt{W/\pi h}$ , where R is the radius of the assumed cylinder. A mean value of R was obtained from height and weight measures of a composite group of 31 men. Eleven representative anthropometric measures were also made on each of the men as indicated in Table 8 and the mean values of each measure were divided by the mean R to derive a constant. In later papers R itself was considered to be a dimensionless constant (D). The summed constants so derived (i. e., mean measures/R) were shown to be a constant amounting to 300. In application of the calculations in reverse, the sum of the measured 11 circumferences divided by the derived constant (300) provides a quotient (R or D) which "in many individuals is nearly identical to the square root of weight divided by stature" (29), i. e.,  $D^2 \times h = W$ . The relationships have been shown to hold with a variety of different groups.

Skinfolds: Since the subcutaneous adipose tissue constitutes more than 10% of the body weight in the normal adult and represents more than half of the total adipose tissue (168), measures of "skinfold" thickness have been widely

TABLE 8

ANATOMIC SITES AND LEVELS MEASURED IN DESCRIBING BODY BUILD

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- Abdomen ( 1 ) --the usual minimal waist circumference between the lower border of the rib cage and the brim of the pelvis
- Abdomen ( 2 ) --level of iliac crests to encompass fat roll when present and, anteriorly, the umbilicus
- Shoulder --maximal protrusion of bideltoid muscles and, anteriorly, at the articulation of the sternum and second rib
- Chest --Nipple line (fifth rib, male) and axillary level (female) measured during the course of normal breathing
- Buttocks --maximal gluteal protrusion and symphysis of the pubis
- Thigh --maximal circumference at the level of the gluteal fold
- Biceps --fully flexed (maximal)
- Forearm --fully extended, hand open (maximal)
- Wrist --distal to styloid process of the radius and of the ulna (minimal)
- Knee --middle of the patella (subject standing with knee slightly flexed)
- Calf --maximal circumference
- Ankle --above malleoli (minimal)
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Source: Behnke, 1963 ( 30 ).

used as indices of body composition. The skinfold so measured includes a double layer of skin and a double thickness of subcutaneous tissue. While manual pinching of skinfolds has been common in clinical practice, particularly in the pediatric field, the use of special graduated calipers has been developed in anthropometric studies and is discussed in detail by Keys and Brozek (168), and Brozek (43, 44), as well as by numerous others quoted in the cited references. Some of the major problems in skinfold measurements lie in defining the requirements for design of skinfold calipers, in selecting the most suitable sites for making skinfold measurements, and in allowing for changes in compressibility with size, age, sex, and duration of maintained pressure. Since the measure is influenced by the amount of pressure applied, and by the area of the contact surfaces, numerous attempts have been made to design calipers in which the pressure applied is consistent over the entire range of operation, and to standardize the amount of pressure so applied and the area of contact surfaces. A study has been made by Edwards and his colleagues in Britain (94), of the various factors affecting the design, and numerous caliper designs have been produced to meet the requirements to a greater or less degree (168). Without making comparative studies it is not possible to select the most suitable. A commonly accepted model in this country is the Lange skinfold caliper.

Standardization has provided some difficulty, but the commonly accepted values allow for an applied pressure of  $10 \text{ gm/mm}^2$  and a contact surface of  $20 - 40 \text{ mm}^2$  (43), both of which are met by the Lange caliper.

The question of appropriate sites of measurement has received considerable attention. Matiegka (213), who was responsible for some of the definitive work in this area, used seven sites, while some of the German workers have used over sixty. The 1956 Committee on Nutritional Anthropometry (232), however, has recommended use of two sites as a minimum, namely, the dorsal skinfold of the upper arm and the subscapular skinfold. The upper arm skinfold is located on the dorsum of the right upper arm over the triceps, at a level midway between the lateral margin of the acromial process of the scapula and the tip of the olecranon, with the crest of the fold parallel to the long axis of the arm. Brozek (44) recommends precise location of the point,

and consideration might be given to having it marked in some semi-permanent manner when repeated measures are indicated. The subscapular fold is measured below the tip of the right scapula, with the crest oriented medially upwards at about  $45^{\circ}$  from the horizontal. Pascale <sup>(249)</sup> and his colleagues, in work relating skinfold thickness and body density in soldiers, have also recommended a site along the mid-axillary line as being a good predictor of total body fat.

The technique by which the procedure is conducted can influence the result. When a fold is lifted, the sides are not parallel. Placement of the caliper near the base will result in too large a measure. Keys and Brozek <sup>(168)</sup> recommend that the caliper should be placed about 1 cm distant from the point where the skin is lifted, and define the placement point on the fold as "the minimal distance from the crest at which a true fold, with surfaces approximately parallel to each other and to the contact surfaces of the calipers, is obtained upon application of the calipers to the skin."

Compressibility of the fold has been shown to be affected by age, and sex <sup>(19)</sup>, although in the astronaut population under consideration here the significance is of minimal account, since the age group is circumscribed in a male population. The skinfold thickness is also increased by superficial edema, and under conditions of exposure to heat in the region of  $120^{\circ}\text{F}$  (Newman, quoted in Keys and Brozek <sup>(168)</sup>). Of interest also is the fact that when pressure is maintained for a minute or more, a slow reduction in thickness occurs <sup>(168)</sup>; consequently measures should be made as rapidly as is consistent with accuracy.

Various equations have been developed relating skinfold values with other body measures for the prediction of fat content, density, or specific gravity. Matiegka <sup>(213)</sup> utilized measures of surface area and skinfolds to predict fat content; Brozek and Keys <sup>(47)</sup> used five skinfold sites in a prediction of specific gravity and fat content; Pascale <sup>(249)</sup> predicted density from triceps and subscapular skinfolds; Chinn and Allen <sup>(59)</sup> used a composite equation involving skinfolds, height, weight, and age as a prediction of fat content, and Young <sup>(351)</sup> used a skinfold measure and the percentage standard weight to determine specific gravity.

Damon and Goldman <sup>(73)</sup> compared the first four of these techniques along with six other anthropometric systems of measurement, including Behnke's <sup>(31)</sup> 11 circumference system, in 13 subjects in whom density was measured by an underwater weighing technique. They found that the method of Pascale et al., <sup>(249)</sup> came closest to predicting body fat, as determined from densitometry, with a mean difference of -1.6% fat.

Pascale used the average of two equations as follows:

$$\text{Density} = 1.0923 - 0.0202 (\text{triceps fold in cm}) \quad (73)$$

$$\text{Density} = 1.0896 - 0.0179 (\text{subscapular fold in cm}) \quad (74)$$

Tied for second place were the Brozek-Keys equations for skinfolds <sup>(47)</sup> and a method of Brozek's involving somatotype values.

It is probable, however, particularly where other measures are being made of body density, that an equally meaningful use of skinfold values will be as a fat index, obtained by simple addition of the measured values, although confirmatory calculations can be done by Pascale's formulae to verify independently obtained findings. In addition, on the assumption that the adipose tissue layer forms a cylinder around a limb, an index of limb muscularity can be obtained by subtracting a value representative of the fatty layer from the measured limb circumference, thus <sup>(44)</sup>:

$$d = \frac{c}{\pi} - \frac{S_1}{2} - \frac{S_2}{2} \quad (75)$$

where d = diameter of limb

c = circumference of limb

S<sub>1</sub> = thickness of triceps skinfold

S<sub>2</sub> = thickness of biceps skinfold

Where the triceps skinfold only is measured, as is common practice, the full value of this skinfold is subtracted instead of the half-value of both.

From the foregoing, it is apparent that anthropometric measurements, including skinfolds, are of value in characterizing various aspects of body composition, and in estimating total body fat. From the multiplicity of potential measures, however, (and by no means all have been considered) it is difficult to select the most useful minimum requirements.

To determine, amongst other matters, valid regression equations

using clinically applicable anthropometric measurements which estimate total body fat, Steinkamp and his colleagues (314, 315) made a comprehensive examination of 2301 healthy Caucasian and Negro individuals of both sexes.

The anthropometric measures, carried out under controlled and regulated conditions, included weight, height, upper arm length, arm circumference, wrist circumference, chest circumference, waist circumference, iliac crest circumference, thigh length, thigh circumference, ankle circumference, bi-acromial diameter, antero-posterior chest diameter, bi-iliac diameter, antero-posterior diameter at iliac crest, thigh diameter, and skinfolds at arm (triceps), right inferior angle of the scapula, anterior axillary line at the 10th rib (thorax), and abdomen. Details of the measurement techniques are provided in their paper (315).

Other measures on 167 selected subjects included body density (helium dilution of Siri) total body water (tritium), potassium ( $K^{40}$ ) activity; and cesium ( $Ce^{137}$ ) activity (80 subjects). Somatotyping according to the photographic technique of Sheldon was undertaken, along with a record of maximum experienced weight (165 subjects). From these, the ponderal and trunk indices were calculated. Total body fat was calculated for each subject from the combined measurements of body density and total body water. Lean body mass was calculated from body weight less total body fat. Selected subjects underwent an evaluation of dietary habit, intake and physical activity.

In the 167 subjects in whom total body water and density determinations were made, regression equations were developed relating anthropometric measures with body fat. The procedure involved an initial calculation using that anthropometric variable which corresponded most highly with body fat. A second equation incorporating two variables, was then derived by including the variable which corresponded most highly with the deviations between the actual and the predicted body fat using the first equation. In other words, the second variable best explained what was unaccounted for by the first equation. Other variables were similarly added. The results are shown in Table 9.

TABLE 9

Two, Three, and Four Variable Regression Equations and Multiple Correlations by Category

After Steinkamp, Cohen, Gaffey, et al. (314).

Category	Number of variables	Estimated fat in kg					Multiple correlation with measured fat in kg
White males 25-34 yr	2	0.647 I.C.C.*	+0.453 Arm S.F.	-43.659			0.939
	3	0.498 I.C.C.	+0.362 Arm S.F.	+ 0.415 Thigh C.	-52.836		0.949
	4	0.372 I.C.C.	+0.249 Arm S.F.	+ 0.449 Thigh C.	+ 0.380 Thorax S.F.	-45.464	0.959
White males 35-44 yr	2	0.573 Waist C.	+0.332 Arm S.F.	-33.286			0.897
	3	0.362 Waist C.	+0.314 Arm S.F.	+ 0.265 Chest C.	-41.093		0.906
	4	0.381 Waist C.	+0.368 Arm S.F.	+ 0.382 Chest C.	- 0.272 Scapula S.F.	-51.268	0.918
White males 25-44 yr	2	0.350 Waist C.	+0.444 I.C.C.	-50.560			0.909
	3	0.367 Waist C.	+0.351 I.C.C.	+ 0.287 Arm S.F.	-46.791		0.926
	4	0.352 Waist C.	+0.395 I.C.C.	+ 0.253 Arm S.F.	- 0.353 Arm Length	-35.689	0.930
Negro males 25-44 yr	2	0.372 I.C.C.	+0.386 Abdomen S.F.	-20.462			0.910
	3	0.342 I.C.C.	+0.289 Abdomen S.F.	+ 0.242 Thorax S.F.	-19.377		0.914
	4	0.333 I.C.C.	+0.212 Abdomen S.F.	+ 0.358 Thorax S.F.	+ 0.515 Thigh Length	-39.408	0.920
White and Negro males 25-44 yr	2	0.320 Waist C.	+0.451 I.C.C.	-48.910			0.900
	3	0.307 Waist C.	+0.410 I.C.C.	+ 0.169 Arm S.F.	-45.994		0.906
	4	0.282 Waist C.	+0.363 I.C.C.	+ 0.136 Arm S.F.	+ 0.175 Thorax S.F.	-41.448	0.909
White females 25-34 yr	2	1.176 Arm C.	+0.635 Thigh C.	-44.255			0.913
	3	0.861 Arm C.	+0.533 Thigh C.	+ 0.147 Abdomen S.F.	-34.949		0.930
	4	0.354 Arm C.	+0.403 Thigh C.	+ 0.159 Abdomen S.F.	+ 0.083 Weight	-26.189	0.937
White females 35-44 yr	2	0.338 Weight	-2.494 Wrist C.	+14.046			0.972
	3	0.283 Weight	-2.216 Wrist C.	+ 0.203 Arm S.F.	+12.125		0.977
	4	0.300 Weight	-1.855 Wrist C.	+ 0.169 Arm S.F.	- 0.511 Arm Length	+23.173	0.980
White females 25-44 yr	2	0.337 Weight	-3.294 Wrist C.	+24.859			0.946
	3	0.363 Weight	-2.710 Wrist C.	- 1.050 Biacromial D.	+49.864		0.963
	4	0.307 Weight	-2.239 Wrist C.	- 0.868 Biacromial D.	+ 0.185 Arm S.F.	+39.358	0.970
White males and females 25-34 yr	2	0.552 I.C.C.	+0.504 Thigh C.	-57.266			0.917
	3	0.377 I.C.C.	+0.489 Thigh C.	+ 0.319 Thorax S.F.	-44.904		0.933
	4	0.380 I.C.C.	+0.588 Thigh C.	+ 0.263 Thorax S.F.	- 0.334 Arm Length	-37.294	0.937
White males and females 35-44 yr	2	0.792 I.C.C.	-0.652 Iliac D.	-32.813			0.914
	3	0.676 I.C.C.	-0.675 Iliac D.	+ 0.338 Thigh C.	-39.297		0.922
	4	0.662 I.C.C.	-0.475 Iliac D.	+ 0.342 Thigh C.	- 0.389 Arm Length	-29.836	0.927
White males and females 25-44 yr	2	0.562 I.C.C.	+0.457 Thigh C.	-55.227			0.914
	3	0.542 I.C.C.	+0.557 Thigh C.	- 0.513 Arm Length	-39.770		0.924
	4	0.515 I.C.C.	+0.317 Thigh C.	- 0.878 Arm Length	+ 0.062 Weight	-20.832	0.929
All subjects	2	0.592 I.C.C.	+0.360 Thigh C.	-53.107			0.905
	3	0.571 I.C.C.	+0.471 Thigh C.	- 0.472 Arm Length	-39.560		0.913
	4	0.489 I.C.C.	+0.439 Thigh C.	- 0.384 Arm Length	+ 0.187 Thorax S.F.	-36.165	0.918

\*I.C.C. = Iliac crest circumference. S.F. = Skin fold thickness. C. = Circumference. D. = Diameter.

From the table, it is apparent, and fortunate, that the highest correlations in males are found in the population age group commonly associated with astronauts, and that the measures involved are relatively simple. Thus, the two-variable equation, with a correlation of 0.939, requires measures of the iliac crest circumference and the triceps skinfold. The three-variable equation, with a correlation of 0.949, requires measures of the iliac crest circumference, the triceps skinfold and the thigh circumference; and the four-variable equation, with a correlation of 0.959, requires the additional measure of the thoracic (axillary) skinfold. These measures, of course, can be readily obtained with a linen tape and a suitable skinfold caliper.

To summarize the requirements of somatometric measures, it is apparent that, in addition to height and weight, which are fundamental to any consideration of body composition, meaningful information can be derived from a few relatively simple measurements which can be readily obtained in a manned orbital space laboratory. The minimum recommended battery of measures would include the 11 circumferences suggested by Behnke<sup>(30)</sup>, which in turn include those circumferences necessary for Steinkamp's regression equations<sup>(314)</sup>. In addition to these, measures of triceps, subscapular, and axillary line (thoracic) skinfolds would provide fat indices, and allow calculation of the various regression equations involving skinfolds<sup>(47, 59, 249, 314, 351)</sup>. Useful additional measures would be the bi-iliac and bi-acromial diameters, as recommended by the Council on Nutritional Anthropometry<sup>(232)</sup>, but since these last noted measures cannot be made with a linen tape and require some form of anthropometer with blades, and, in addition, would not be expected to change, the justification is doubtful.

#### Radiographic Techniques.

After a late start in the thirties, much consideration has been given to the use of radiographic analysis in the estimation of body components, particularly the subcutaneous fatty layer. A comprehensive review of the subjects presented by Garn<sup>(121)</sup>, who has been very active in the field.

While accepting the possibility that radiographic facilities of some sort may be available in a manned space laboratory, it is expected that they will be somewhat limited, and unlikely in the foreseeable future to meet the demanding requirements of radiogrammetry. In addition to the technical requirements of the apparatus, one of the major problems lies in standardizing the positioning of the subject with respect to the tube, or the film with respect to the tube. The greater the distance between tube and film, the less magnification occurs in the film from displacement of the midplane of the subject from the film. Garn <sup>(121)</sup> has compromised on a 6 ft. anode to-film separation, which in turn requires some 10-12 ft. of available space. Tanner <sup>(322)</sup> maintains a fixed tube-to-subject distance of 2.5 meters which requires still more room. In addition, the technique, for accurate measurement, calls for "soft-tissue" exposures using high speed film, parspeed screens, and a peak voltage of 30KV plus twice the part thickness in centimeters, at 7-15 MAS <sup>(121)</sup>. Thus, it is considered unlikely that radiographic techniques will be applicable. A brief review of measurement procedures, however, is in order.

The purpose of the radiograph is of course to obtain accurate and repeatable measurements of fat, muscle, and bone shadows. Consequently the site or sites selected are influenced by the requirements, and the opportunity of observing correlations with other measures in the same region. Brozek and Mori <sup>(48)</sup>, in examining relationships with body density, have used the upper arm, forearm, thigh, and leg; Tanner <sup>(322)</sup> has used the upper arm, thigh, and calf; and Reynolds <sup>(270)</sup> has used the limbs; while in a comparative study, Garn <sup>(120)</sup> showed that the highest covariance with body fat, and correlation with body weight, was found at the trochanteric site, the iliac crest, and the lateral thorax at the level of the 10th rib. Other factors influencing site selection are the technical difficulty of radiography at the site, the likelihood of positioning error, the presence of underlying landmarks, and the size of the measuring error relative to the median fat thickness <sup>(121)</sup>.

Accuracy of positioning for radiography at a given site is critical. For the most part, antero-posterior, and postero-anterior, or exact

lateral projections are employed, with care being taken to avoid rotation. To minimize gravitational distortion in the terrestrial situation it is common, where possible, to maintain the subject in the vertical position. Gravitational distortion would of course not be a problem in a space laboratory.

Linear measurements are made on the exposed and processed film along a line perpendicular to the skin surface, commonly by way of a sharp-pointed caliper. Measurement difficulty arises from the fact that the boundaries between background, skin, fat, and muscle are never sharp. In this connection Garn <sup>(121)</sup> notes wryly that the pin-point holes made by the calipers tend to improve inter-observer reliability in measurement.

Good correlations, in the region of 0.8 to 0.9, have been reported between radiographic fat thickness, skinfold thickness, and fat weight, and even higher correlations (0.92 to 0.97) between radiographic thickness and the area or volume of the fat in the region examined <sup>(121)</sup>; but while equations can be developed for predictive purposes, it is probable that, as with skinfolds, a better object is served at this time by maintaining the data in a raw form. As Garn <sup>(121)</sup> remarks: ". . . . one may convert fat-shadows into skinfold equivalents, and these in turn, into densitometric estimates, achieving at the far end of the equation some sort of fat estimates, or, one may pair fat-shadow and densitometric values, guessing at body composition through the mutual relationship. Finally, it is possible to start afresh, converting fat and changes in fat, into estimates of fat tissue weight and changes therein. . . . (but). . . . 30 millimeters of iliac, trochanteric, or lower-thoracic fat are not directly translatable into kilograms of fatty tissue."

In addition to its use in bone shadow width measurement, radiography may be used in the estimation of bone density. Pauline Mack has been the prime exponent in this field. The optical density of the radiographic negative is related to the mass of mineral in the bone. To obtain quantitative measures, however, allowance has to be made for the effect of factors such as bone size, the absorption of soft tissues and the effect of the organic bone matrix <sup>(207)</sup>. The technique entails radiographic

scanning of the bone under consideration (recently the os calcis and a digit <sup>(208)</sup>), along with simultaneous scanning of a calibrated aluminum wedge. The equipment in current use is complex and bulky. In its early stages <sup>(205, 206)</sup> the method utilized a microphotometric scanning procedure with manual planimetry of the resulting trace and extensive mathematical processing. Recent developments have largely automatized the procedure <sup>(207)</sup>. Since different exposures must be used to accommodate different part thickness, and since the resulting film density is also affected by factors such as wavelength, intensity of exposure and film processing conditions, the relationship between optical density and bone density is non-linear. The processing equipment is designed to correct the density curve to a linearized exposure curve so that scale deflection of the instrument becomes a direct function of x-ray absorption. The wedge pattern obtained on the film reflects film exposure and processing conditions so that its density curve produces necessary data for correcting the bone scan for integration purposes, as well as providing a means of determining comparative x-ray absorption.

Experiments with the apparatus have shown that it can be used for integrating bone areas accurately from x-rays derived from a broad range of intensity values, namely, from 10-80 MAS, with a standard deviation of 0.024 gm equivalents of calcium phosphate-carbonate per cc of bone, as derived from calibration of the wedge <sup>(207)</sup>. The technique has also been used for pre- and post-flight evaluation of Gemini Astronauts <sup>(208)</sup> with demonstration of variable loss in bone density associated with space flight conditions. Because of the requirement for advanced radiographic facilities, along with the complexity and bulk of the equipment, and the demands of rigorous technique, it does not seem reasonable at this time to consider its use on-board a manned space laboratory. It might, however, be feasible to utilize standard on-board x-ray equipment combined with a photoscanner from which the resulting voltage signal could be telemetered to ground for processing. The possibilities of this approach do not seem to have been investigated.

## Ultrasonics

Another instrumental technique that has been used in the evaluation of body masses, particularly fat thickness, is that of ultrasonic scanning. This technique has found particular favor in animal work to determine fat thickness of animals on the hoof. Alsmeyer and his colleagues <sup>(13)</sup>, among half-a-dozen groups of veterinary workers in this country, showed moderate correlations (0.6 to 0.8) in swine and cattle between back fat measured directly and by ultrasonic scan. A still broader review is provided by Stouffer <sup>(318)</sup>. Although ultrasonic scanning techniques are used in human investigation for other purposes, very little work has been done with the ultrasonic techniques as a measure of fat thickness in humans. Bullen and coworkers <sup>(49)</sup> in Denmark, with an echo-ranging encephalograph ultrasonic instrument, undertook a study to compare fat folds, as measured by the instruments, with those obtained by Lange skinfold caliper and by needle puncture. They used the triceps, subscapular, and abdominal sites. A high coefficient of reliability was found between repeated ultrasonic measurements (0.985 to 0.994) and between ultrasonic and needle measures (0.98), while good agreement was observed with caliper measures (0.8 and 0.9). However, while the technique obviously has validity and potential it would seem to hold little, if any, advantage over simple skinfold measures, in view of the complexity and bulk of the necessary instrumentation.

## Inert Gas Absorption

Still another process has been examined by Lesser and his colleagues <sup>(186, 187)</sup> in an attempt to devise an independent and primary method of body fat estimation. They determined initially the quantity of body fat in the rat by observing the body uptake of the inert but highly fat soluble gas cyclopropane. At equilibrium in a closed system the tissues contain the gas at the same partial pressure as in the respiratory system, and after correction for the small amount of gas absorbed in the non-fatty tissues, the remainder of the gas absorbed divided by the solubility coefficient of the gas in rat lipid provides a measure of body fat. Unfortunately, in man, even after 6 - 8 hours of exposure, equilibrium is not attained, and graphical and mathematical

extrapolations have to be made. In addition, the cyclopropane absorption curves were found to show appreciable variation in gas uptake rates with time. To assist in reducing these problems, Lesser and Zak (188) developed a technique using two gases, cyclopropane and krypton, with different solubility and diffusion properties. The results obtained with these gases agreed very well with measures of the fat-free lean mass calculated from total body water (mean difference  $1.74 \pm 3.87\%$ ). The instrumentation, however, is highly complex, with a requirement for a closed respiratory system, pump, intricate plumbing, and devices for gas analysis. In addition, the subject time is prolonged (6 - 8 hours). In fact, the investigators themselves remark: "It is a long and somewhat uncomfortable experiment." Despite its usefulness in providing an independent method of estimating body fat it is obvious that for the foreseeable future the technique has no place in a manned orbital laboratory.

From the foregoing, it is apparent that while radiography, ultrasonics, and the use of two-gas systems for fat estimation have much to offer in the terrestrial laboratory or even in advanced clinical studies, the complexity of the apparatus and the rigorousness of the techniques is such as to render them inappropriate for space-borne use in the foreseeable future, particularly since most of the information so obtained can be derived by other methods. An exception to the latter statement is the bone density measurement, which would be valuable, but meantime does not seem practicable for space-borne use. Perhaps with further development it will become so.

#### Multiparameter Concept

The multiparameter, or functional, concept in the evaluation of body composition owes its origins to the work of Moore and his colleagues (228) in determining the nature of the body cell mass and its relationships to its supporting structures and body fluids.

By this concept, the body cell mass is a "homogeneous oxygen-requiring, carbon-dioxide-producing, glucose-burning mass of tissue. It contains no fluids other than its intracellular water. It contains no solids outside of the

cell membrane. It has no function of support or transport other than within the cell itself' (228). The lean body mass and fat free body in contrast are heterogeneous, and include the heavy and dense material of the skeleton, as well as a large volume of water outside the cells which is presumably constant in health but variable in disease, obesity, or wasting.

All body cells contain potassium ( K ) in a more or less constant concentration. The total potassium content of the human adult male is 50 to 54 mEq per kg of body weight (103) or 150 mEq per kg of cell water (228), of which about 90% is intracellular. Furthermore 90% of the intracellular K is in muscle cells (348). As will be discussed, there is more than one method of obtaining a value for total body potassium, but it has been shown by Moore and his colleagues, and others, that after a 24 hour period for establishment of equilibrium, the distribution of the radioisotope  $K^{42}$  measures about 98% of the body potassium (228). The unmeasured fraction is represented by the slowly exchanging component of erythrocyte potassium, and perhaps some slowly exchanging potassium in the central nervous system.

To derive a value for the body cell mass from measurement of exchangeable potassium it is assumed that the potassium-nitrogen ratio in wet cellular tissues is 3 mEq per gm., and that the coefficient for calculation of wet tissue from nitrogen is based on a factor of 25. Thus, the total weight of the wet body cell mass in gm is equal to the value of the exchangeable potassium ( $K_e$ ) in mEq multiplied by 8.33. Moore admits that the figure of 8.33 is somewhat arbitrary and represents an estimate between 7.5 and 9.5 (228).

The intracellular water is another component of the body cell mass. Unfortunately it does not lend itself to measurement and must be calculated from the difference between the total body water and the extracellular water. Two other considerations require examination. One is concerned with the relative hydration of the body. Changes in observed hydration may result from loss of body cell mass alone. In this situation, the fat-free body undergoes an alteration in the distribution of water and solid tissues. There

may be loss of body cell mass while the extracellular tissue and fluid compartments are maintained intact. On the other hand the body cell mass may remain constant while a great increase takes place in extracellular water; or there may be some combination of both with no relative change. In all cases, however, there is a change in the ratio of intracellular water to total body water (ICW/TBW).

The second consideration concerns the relationship between exchangeable potassium ( $K_e$ ) and fat free solids (FFS). FFS are defined as that component which is represented by the fat-free body minus the total body water. The intracellular solids are characterized by a high potassium content, while the extracellular tissue solids are characterized as being fat-free solids associated with a minimum amount of potassium, among which the skeleton predominates as a dry bone matrix with mineral. Moore and Boyden<sup>(228)</sup> point out that the relative weight of the skeleton in the body can be regarded as an inverse function of the  $K_e$ /FFS ratio. On this basis, they developed a nomogram from which dry fat free bone weight can be estimated from knowledge of  $K_e$  and FFS (figure 17). As the body cell mass and body fat waste around a skeleton of fixed size, the  $K_e$ /FFS ratio falls and the relative weight of the skeleton rises. It is apparent, however, that where the skeleton mineral is also being mobilized the relationships will not hold true.

Nevertheless, normally the body cell mass is defined by the total exchangeable potassium and total intracellular water. The supporting environment is represented by the sum of the extracellular water, the extracellular solids (including the skeleton) and total body fat.

The work of Moore, and those who have followed him, has relied upon the facilities supplied by well equipped radioisotope and analytical laboratories, where measures could be made, using the dilution principle, of the various functional components of the body, taken more or less within the same short time period, in such a manner that they could be related one to the other.

The measures to be made include total body water, total exchangeable potassium, total exchangeable sodium, total exchangeable chloride, plasma

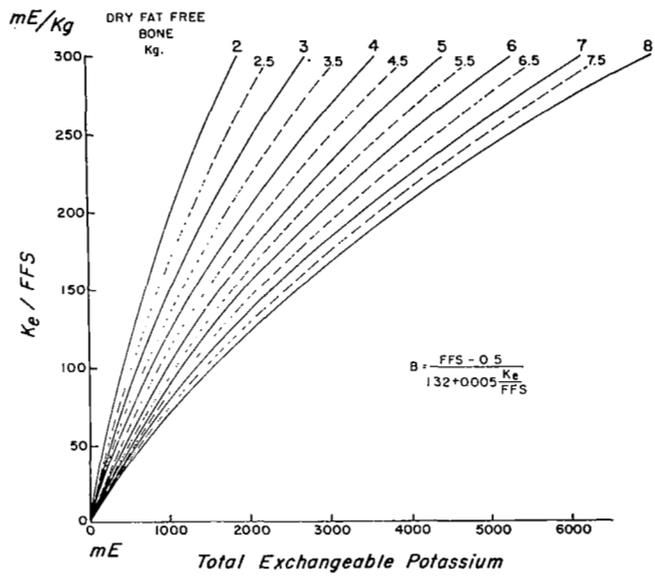


Figure 17. Prediction of skeletal weight. Nomogram is entered with observed  $K_e / FFS$  and observed  $K_e$ . The estimated skeletal weight is then read off a family of lines.  
 After Moore and Boyden (228) ).

volume, red cell mass, and body weight. The body cell mass is derived from the total exchangeable potassium ( $K_e \times 8.33$ ); the extracellular fluid is derived from the bromide (chloride) dilution volume, the intravascular component is obtained as the sum of the plasma volume and the red cell mass; the intracellular fluid component is given by the difference between the total body water and the extracellular component; the fat free body is derived from the total body water on the basis that the fat free body is 73.2% water<sup>(245)</sup>; total body fat is obtained from the difference between body weight and the fat free body, while fat free solids are represented by the difference between the fat free body and total body water. The estimated skeletal weight is then derived from the  $K_e$ /FFS ratio. The ICW/TBW and the  $Na_e/K_e$  ratios reflect the balance between the extracellular and intracellular phases.

McMurrey and his colleagues<sup>(218)</sup> from Moore's group have described in detail the procedures and time sequencing required in making the various measures. Although there have been some refinements from time to time, the apparatus essentially comprises a well-type scintillation counter, a flame photometer, a photoelectric colorimeter, a vacuum distillation and falling drop apparatus, a plastic bag and filter, blood recipient set, a pressure device for blood transfusion, and calibrated syringes, along with supplies of suitable agents. The combined procedure is divided into three phases requiring a total of 48 hours, and necessitates a series of eight intravenous injections given to subjects who initially fast for 8-10 hours prior to beginning the test. Urine and other waste collections are obtained throughout.

Manifestly the procedure as practiced by Moore is not feasible in its entirety in a manned space laboratory. Questions arise, however, as to how much is useful and feasible, and how necessary is the requirement for radioisotope studies. Each of the major determinations will be examined with this in mind. Fundamentally there is no doubt that in terrestrial conditions with adequate facilities, methods employing radioactive tracers are inherently more accurate and sometimes simpler than methods requiring estimation of the volume and distribution of an added chemical, which may be metabolized or handled differently from the chemical whose volume and

distribution it is intended to duplicate. The volume and weight constraints within a spacecraft, however, militate against the addition of complex devices for the detection, amplification, and display of radioisotope data, particularly where the problems imposed by the inherent bulk and weight of the apparatus are aggravated by the necessity for heavy shielding of scintillation tubes, shielding, in some cases, of stored isotopes, and perhaps the necessity for maintaining maximum distance between stored radioactive materials and the detection apparatus, or other sensitive equipment.

The principle of the dilution method is based on the relationship

$$V_2 = \frac{C_1 V_1}{C_2} \quad (76)$$

where  $C_1$  and  $V_1$  are the concentration and volume of the solute before dilution, and  $C_2$  and  $V_2$  are the concentration and volume of the solute after dilution. Knowing  $C_1$  and  $V_1$  and measuring  $C_2$  allows for calculation of  $V_2$ . Keys and Brozek<sup>(168)</sup> have defined the requirements for an ideal test substance. It should rapidly penetrate and dissolve or mix evenly in the appropriate body fluid; it should not be absorbed on, be combined with, or be destroyed by other constituents of the body, or at least such deviations from distribution exclusively as a simple solution in water must be constant and predictable; it must be eliminated from the body at a precisely measurable rate, not be toxic in the amounts needed, and be readily and accurately measurable. All the requirements are rarely met in one substance.

#### Total Body Water

The material that appears to meet most of the requirements as a test solute for total body water is deuterium oxide ( $D_2O$ ). It is non-radioactive, and non-toxic in the required dosage. Distribution is more or less complete throughout the body fluids, and only a minimal exchange of hydrogen occurs, allowing for less than 1.5% of the deuterium administered<sup>(91)</sup>. Negligible loss occurs during the equilibrium period and the dilution curve after mixing is essentially flat.

The solute is administered orally in the basal state (no food or water for 12 hours previously) and sampling made on the urine over a period of 3 hours. Testing requires extraction of a pure water and D<sub>2</sub>O sample from the urine by a freezing and vacuum distillation process before measurement. In terrestrial conditions, measurement is commonly made by the "falling-drop" method, by which the differential density of water and a D<sub>2</sub>O sample is measured while falling through a solution of orthofluorotoluene (292). Since the method requires a gravitational vector it is inapplicable in weightlessness. However, even more accurate measurement can be made by a mass spectrometer (311), and it is possible that an osmometer method could be developed.

Deuterium presents no storage problem, but, because of the biological half-life of about 12 days, repeat measures would not be practicable for at least 2-3 weeks without doubling up on the dosage. Normally repeat measures are not made before a two-month interval.

Failing the presence of a mass spectrometer, or the development of a suitable osmometer measurement, tritium might be considered a test solute (246). Tritium is a radioactive  $\beta$ -emitter with a half-life of 12 years, although its biological half-life in the body is only about 12 days. Studies with tritium (257) have shown results similar to those with deuterium. Its use, however, is grossly complicated by the requirement for measurements of radioactivity. Normally measurement is conducted by way of a liquid scintillation system. After oral administration and collection of equilibrium urine samples, the urine is either filtered through activated charcoal, or better, freeze distilled. One ml of the sample is then added to 19 ml of the scintillation fluid which is placed in a container within the counter chamber of the scintillation counter and counted for a suitable time (approximately 10 minutes). Calibration counts are made with a blank containing a known amount of tritium. A common scintillation counter consists of two photomultiplier tubes with plastic scintillation phosphors separated by a counter chamber. The tubes are heavily shielded with approximately 3" of lead. Pre-amplification electronics are included in the tube module. The signal is lead to further amplification and processed for digital or other display. Boling (38 )

describes a standard device. There is no doubt that special design could minimize the bulk of the apparatus. A major constraint, however, would still be the weight imposed by the lead shielding of the tubes.

Since tritium is a low energy  $\beta$ -emitter there is little problem in storage, which may be undertaken in ordinary glassware. Repeatability of the measure is again determined largely by the biological half-life of 12 days. However, doubling of the dosage is inherently more hazardous than doubling of the dose of deuterium.

Other non-radioactive methods have been used for the estimation of total body water. According to a review by Pace and his associates (246), sulfanilamide was proposed as a test substance but later rejected because of unequal distribution in body tissues. Urea was suggested, but was rejected because of the variability in the formation of endogenous urea, as well as because of unequal distribution. In this regard, however, Keys and Brozek (168) draw attention to later studies in which the urea method compared favorably with direct analysis, and with deuterium results, and consider that rejection of the urea method is unjustified.

The most common of the chemical methods has involved the use of the pyrolozoles, namely, antipyrine and its derivatives, 4-aminoantipyrine (159) and N-acetyl 4-aminoantipyrine (41). The pyrolozoles are non-toxic in the dosage used, uniformly distributed in the tissues, and provide results more or less equivalent to those from deuterium oxide (309). Some metabolism of antipyrine, however, does take place and there is a tendency towards binding of the antipyrine by protein (309). These discrepancies can be allowed for in calculation, but it is simpler to estimate the theoretical instantaneous concentration of antipyrine at the time of administration by graphing the concentration measured at repetitive intervals and extrapolating backwards the straight line portion of the plot to the zero time intercept (95).

The procedure entails the intravenous injection of antipyrine to a subject in the basal state, followed by serial blood samples for up to 3 hours. A single blood sample could suffice. After processing of the samples, the concentration is obtained by an ultraviolet spectrophotometer. A micro-technique is available and full details of the procedure, processing and measurement are presented by Friis-Hansen and his associates (111).

The use of alcohol has been suggested in the past, and has recently been re-examined (252). The method depends on the fact that 1 - 1½ hours after ingestion of ethanol (0.35 gm/kg body weight) the concentration in body water, blood, and urine is practically the same. Extrapolation back to zero of a plot taken over three hours (as for antipyrine) gives the theoretical concentration of ingested alcohol in the total body water at the time of ingestion. After moderate water loading the bladder is emptied and alcohol ingested. The bladder is emptied at 1 hour and the urine discarded. Thereafter half-hour samples are analyzed for the next 3 hours. Numerous simple techniques are available for alcohol analyses. If available, gas chromatograph or mass spectrometer can be used. The method is very simple and shows considerable promise, and no doubt would be well accepted by the subjects.

#### Extracellular Water

Extracellular water which, by definition, is the total body water less the intracellular water, is found in five phases, namely, plasma, interstitial-lymph, connective tissue - cartilage, bone, and transcellular fluid (90), which are determined both as anatomical entities and by the readiness of inter-exchange among phases. Plasma volume is an obvious anatomical entity, while the interstitial-lymph fluid is both an anatomical entity and is readily penetrable by test substances. Connective tissue and bone, although containing extracellular fluid, provide a hindrance to rapid diffusion and contribute to the non-exchangeable or slowly exchangeable components. The transcellular fluid compartment includes a variety of extracellular fluid collections, which are not simple transudates of plasma but have the common property of being found in the exocrine glands, the liver and biliary tree, the kidneys, the eyes, the cerebrospinal fluid, and the gastrointestinal tract.

Electrolyte ions, sodium, potassium, and chloride, are distributed throughout the extracellular fluid, but in quantities that differ according to the different phases. The test substances, dependent on their type, may be distributed like the ions or independently of them. Distribution of

body ions is illustrated in figure (18). This figure represents the quantitative distribution, as derived from a variety of measurements by the dilution principle and from direct cadaver analysis. Since the available test solutes penetrate the "spaces" to varying degrees and only equilibrate with the volumes to which they are exposed it is unfortunate that measurements of the various volumes or "spaces" cannot, in some cases, be made as anything other than estimates.

A variety of materials have been used as test substances, but essentially they are of two types, namely, the saccharides, such as inulin, raffinose, sucrose, and mannitol, with large molecules of high molecular weight, and the ions, such as thiosulfate, sulfate, thiocyanate, chloride, bromide, and sodium, with smaller molecules.

Two phases of inulin, sucrose, and thiosulfate penetration have been distinguished (348); an early phase with a half-time of 20 minutes or less, which is probably associated with penetration into the plasma-interstitial fluid-lymph space, and a more prolonged phase with a half-time of 5-9 hours, perhaps associated with penetration of the connective tissue, although in the case of inulin it may be due to accumulation of inulin within the macrophages. The "rapidly equilibrating space" so measured, however, is considered to comprise the plasma and interstitial-lymph spaces, plus that portion (60 to 80%) of connective tissue water penetrated by the test solutes within less than 12 hours (348). Even within that definition, however, there are differences in the volume measured, dependent on the method used.

The amount of exchangeable sodium in man as determined by isotope dilution is much less than that determined by chemical analysis, and averages about 41 mEq per kg of body weight. The non-exchangeable sodium fraction is located in bone, which makes up from 40-45% body weight. Between 20 and 35% of bone sodium exchanges with radiosodium in 24 hours, after which the exchangeable pool increases by about 1% per day (348).

Chloride is the predominant anion in the extracellular fluid and is also found in the cells, with the concentration dependent on the membrane potential, amongst other factors. About 50% of the chloride is found in plasma and

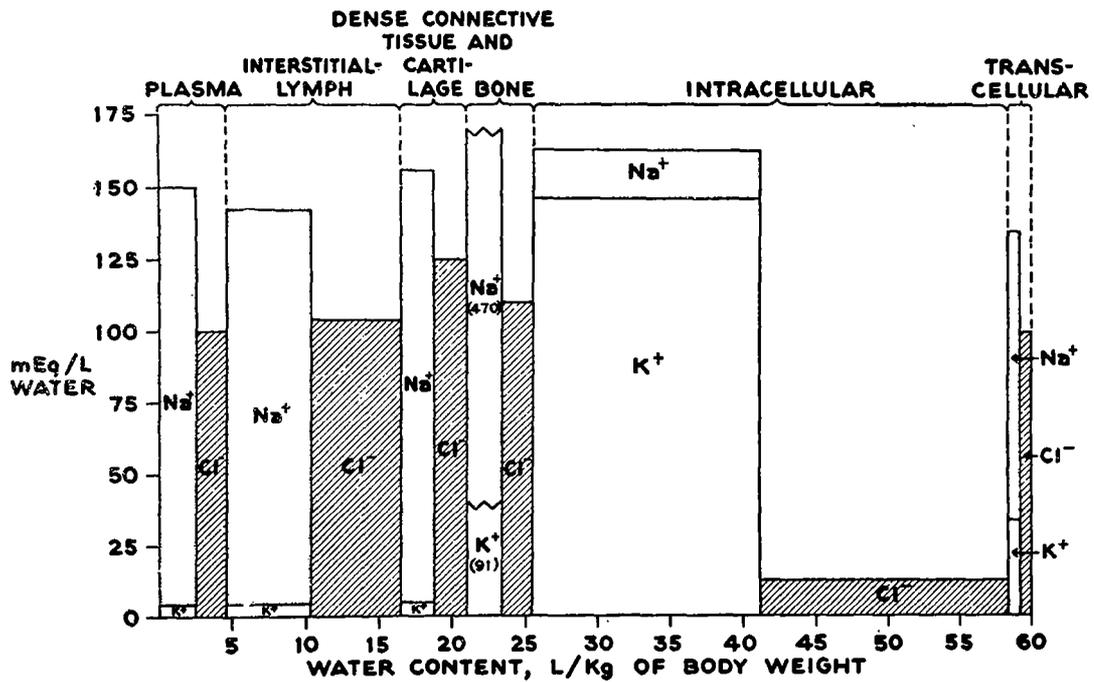


Figure 18. Composite body water composition in an "average" normal young adult male.

After Edelman (90).

interstitial fluids, and about 16% in connective tissue. Most of the intracellular chloride is found in cells with low membrane potentials such as smooth muscle, exocrine glands, glia, connective tissue and erythrocytes. Most of the chloride is rapidly exchangeable however (348). Chloride has been commonly used to represent the extracellular space but because of its widespread distribution and its rapid exchangeability it provides only a rough approximation of the extracellular fluid volume. Similarly, the extent of the volume that is measured by radio-sodium is not too easily definable.

Radiosodium, as  $\text{Na}^{24}$ , with a half-life of about 15 hours, is used in routine estimates by Moore's group (218) and others. Because of the very short half-life of chloride isotopes (about 30 minutes),  $\text{Br}^{82}$ , which has a half-life of about 36 hours, is used as a substitute. The bromide volume is determined from a 14 hour equilibration sample of serum and urine by counting in a well-type scintillation counter. The extracellular volume is calculated from the bromide volume by correcting for the plasma volume, the red cell bromide penetration, and the Donnan effect. Total exchangeable chloride is derived from the bromide volume after determining the serum chloride concentration by spectrophotometry. Total exchangeable sodium is also determined by serum and urine counts at the 24 hour equilibration level, after again determining the serum and urine concentrations. Full details of the techniques are found in the paper of McMurrey and associates (218).

While these techniques are suitable for terrestrial conditions with regular resupply of radioisotopes, the half-lives of the respective isotopes ( $\text{Na}^{24}$ ,  $\text{Br}^{82}$ ) are such that only a single determination of each could be made in a manned space mission, and then only within the first few days of a mission. Consequently the methods cannot be considered feasible for the type of mission envisaged in this study.

Use of the non-radioactive saccharides also presents problems, although inulin with its large molecular weight and lipoid insolubility has certain advantages, namely, that it does not readily penetrate the connective tissue and bone and consequently can be used to give a good estimate of the interstitial-lymph space. In a review of the use of inulin, Gaudino and Levitt

( 125 ) observe, with data and information from various sources, that inulin does not penetrate erythrocytes, diffuse through the normal renal tubule, or undergo concentration by liver cells. It is physiologically inert and exerts negligible osmotic pressure per gram of substance. It is, however, rapidly excreted by glomerular filtration and therefore cannot be used for body water determinations by way of a single injection. The procedure thus depends on maintenance of a continuous infusion until equilibrium is established ( 2-3 hours ), followed by discontinuation of the infusion and collection of urine samples. The requirement for continuous infusion renders the technique largely infeasible for the conditions expected in a manned space laboratory.

Consideration therefore must be given to the use of suitable ions, such as thiosulfate and thiocyanate, which, when injected, permeate the extracellular space in a predictable manner. Gilman and his associates ( 128 ) showed that the equilibrium volume of thiosulfate distribution is akin to that of the extracellular fluid, that the rate of disappearance after equilibrium is proportional to the concentration, that it diffuses rapidly, and that it is metabolized slowly and exponentially. Studies on animals and man ( 54, 55 ) have shown that after intravenous infusion of 12 gm of sodium thiosulfate over a period of about 10 minutes, and collection of 4-6 blood samples over a period of one hour, the volume of the thiosulfate space so derived is of the same magnitude as those for bromide and sodium, but larger than that of inulin. The volume is derived by plotting the analyzed values for thiosulfate on semi-log paper and extrapolating back to zero time. Analysis is done by wet chemical methods, and a micro-technique is available. Full details of the procedure are presented in the paper by Cardozo and Edelman ( 54 )

The thiocyanate ion has been used with success in measuring extracellular water and, in fact, was one of the original methods as propounded by Crandall and Anderson ( 71 ), although it has been used in man on other occasions since ( 82, 154, 185 ). The thiocyanate space represents about 90% of the bromide space ( 132 ). The method involves the intravenous injection of a known amount of sodium thiocyanate ( e. g. , 20 ml of a 5%

solution) followed by collection of blood samples over a period of three hours. Equilibration is normally complete in about 2 hours. For estimation, a re-agent containing distilled water and trichloroacetic acid is added to 1 ml of the serum. After mixing and standing for about 10 minutes the mixture is filtered and 5 ml of ferric nitrate solution is added. An orange color develops which is measured colorimetrically at 469  $m\mu$ . Since the thiocyanate reaction is very much more simply performed and lends itself to photometric techniques, it obviously has great advantages over the thiosulfate method.

### Blood Volume

One of the major components of the body is the blood volume, which includes a large part of the extracellular fluid volume as well as cells. The blood volume is the sum of the volume of cells and the plasma, inside the circulatory system. This definition does not include the extravascular components, and strictly does not allow for penetration of the plasma into the interstitial fluid.

Measurement calls for estimation of both the plasma volume and the cell volume independently, or of the total blood volume. No satisfactory measure has been found for total blood volume other than the impractical method of exsanguination, and even that is limited in its accuracy. A host of methods, however, have been described for cell and plasma measurement. Gregersen and Rawson <sup>(139)</sup>, in a review, list over 30 different methods. Out of these, however, a few have become accepted. For plasma volume, dye dilution or the use of certain radioisotopes is normally considered standard procedure.

Beginning with the use of Vital Red and Brilliant Vital Red in 1915<sup>(167)</sup>, the dye method evolved to the selection of the diazo dye T-1824 or Evans Blue (the number refers to the positioning of side chains) by Dawson and his associates in 1920 <sup>(76)</sup>, and development of a plasma volume measurement technique using spectrophotometric analysis by Gregerson and his associates <sup>(138)</sup> in 1935. The latter group, in developing their technique, observed that the problems of dye estimation with various dyes were

related to the inherent color of the plasma, the presence of hemoglobin and lipemia, and, in repeated estimations, the presence of residual dye. If the residual dye is large in amount, the uncorrected volume may be as much as 25% above the true value, while if there is significant hemolysis a determination cannot be made with a simple colorimeter. In addition, spectral absorption curves of various vital dyes in water, saline, and plasma solutions give rise to errors, if water or saline is used in preparation of standards.

Spectrophotometric analysis, using a dual beam for comparison with a blank and cancellation of interference, overcomes much of the problem, while measurement at a wavelength (620  $m\mu$ ) where the presence of hemoglobin contributes relatively little to the optical density greatly reduces the significance of the hemolysis. In addition, it has been shown<sup>(266)</sup> that T-1824, in comparison with more rapidly disappearing dyes is firmly bound to the plasma albumin.

The actual technique requires intravenous injection of the dye in a dosage of 0.3 mg/kg body weight. At the time of injection, a 10 ml sample of venous blood is drawn for preparation as a reference (dye-free) source. Ten minutes after injection a second blood sample is drawn from the other arm. The dye-free sample and the dyed sample are both centrifuged. Aliquots of plasma from each sample are scanned in a dual beam spectrophotometer, which measures the optical density at 620  $m\mu$ . A single beam spectrophotometer could be used for the purpose, but in that case the unknown and the control are read in succession and the light source must be held to constant intensity by a carefully controlled power pack to obtain accuracy. If the background color is high, as for example from residual dye, the differences in dye concentration between control and unknown may be underestimated<sup>(139)</sup>.

The plasma volume can be calculated from one 10-minute sample; greater accuracy can be achieved, however, by collecting and measuring samples over a longer period, plotting the time-concentration curve on a semi-log-graph and extrapolating backwards to zero time to allow for the loss rate. Loss rate in man closely approximates an exponential curve.

Serum albumin tagged with the radioisotope  $I^{131}$  has also been used in the estimation of plasma volume. The procedure, introduced by Gibson and his associates <sup>(127)</sup>, follows the general lines of the Evans Blue (T-1824) procedure, except for handling and counting. The solute is injected in the form of radio-iodinated serum albumin (RISA) and samples are collected. After preparation, the activity of the  $I^{131}$  is counted in a well-type scintillation counter and the plasma volume calculated from the difference in the counts before and after injection. It is apparent that the storage, handling, and counting procedures, introduce complexities that can be avoided with the use of dyes. Other tags have also been used.  $I^{131}$  has a half-life of about 8 days, and while useful activity might still be present after about 6 weeks storage, the same cannot be said for the other iodine isotope in common use, namely, iodine  $I^{132}$ , which has a half-life of about  $2\frac{1}{2}$  hours. Radiobromide has also been used as a tag for serum albumin, while radioactive chromic chloride has been employed as a test substance which does not act directly as a tag but binds itself to plasma proteins to the extent of 98% <sup>(135)</sup>. However, as Edelman and his associates <sup>(91)</sup> comment: "The tagged albumin methods have yet to show themselves better in theory or practice than the time-honored dye."

The other component of blood volume is the blood cells. For measurement of the red cell mass two approaches are used, namely, radioactive isotope tagging and carbon monoxide uptake, neither of which lend themselves readily for use in a space vehicle. Of the radioisotopes, iron, phosphorus, and chromium have all been used. Radioactive iron, however, requires prolonged feeding experiments over many months, or the injection of donor cells <sup>(126)</sup>, while phosphorus ( $P^{32}$ ) also requires the injection of donor cells, and in addition has a loss rate in man of about 6% per hour which makes it necessary to measure several samples and develop a time-concentration curve in assessment.

Consequently radioactive chromium has become the material of choice. This isotope was introduced by Gray and Sterling <sup>(131)</sup> in 1950 in the form of  $Na_2Cr^{51}O_4$ . It is a soft x-ray emitter with a half-life of 26.5 days. It is readily taken up by red cells in vitro and binds with the globin portion

of the hemoglobin molecule, being slowly eluted at a rate of 1% per day. Since there is no significant loss of chromium to the plasma during the first 24 hours a single sample taken after circulatory mixing is adequate for measurement and calculation. Re-incorporation of eluted isotope into the red cells apparently does not occur. With doubling of the dosage the measure could be repeated if necessary, after about 30 days. The technique, however, is complex, and a well-type scintillation counter is required. For implementation, according to the technique of McMurrey<sup>(218)</sup>, a sample of 45 ml of venous blood is withdrawn in a heparin wetted syringe and injected into the plastic bag containing about 50 millicuries of Cr<sup>51</sup> in 5 ml saline. The bag and contents is incubated for 45 minutes at 37°C with frequent mixing. Incubation is followed by 10 minutes of centrifugation at 1500-2000 rpm after which the supernatant fluid is removed, the cells washed in saline, and recentrifuged. The saline wash is removed and discarded, and the washing process repeated twice more, following which the tagged and washed cells are resuspended in 75 ml of saline, filtered and transfused back into the subject. It has been suggested, however, and the suggestion seems eminently reasonable, that a simpler procedure would involve collection of a 45 ml blood sample, addition of 50 millicuries of Cr<sup>51</sup> to the sample, mixture of the two for about 4 minutes, and re-injection of the mixture. Ten minutes after infusion, a 10 ml blood sample from the other arm is collected, hemolyzed by the addition of 250 ml of distilled water and counted in a well-type crystal scintillation counter in 10 ml aliquots. It might be noted that the electronics and display of a liquid scintillation counter and a well-type crystal counter are essentially the same. If necessary, the same unit can be used with different "modular" counting devices.

For calculation, a measure of the venous hematocrit is also required. It can be determined from the original blood sample. The red cell volume is given by:

$$RCV = \frac{C_i}{C_c \times 100/Hct} \quad (77)$$

where RCV = red cell volume in ml

$C_i$  = total count injected in suspension

$C_c$  = counts per ml of circulating red blood cells after  
equilibration

Hct = hematocrit

In addition to the complexity imposed by the preparation and counting procedure, the use of  $Cr^{51}$  in a manned space laboratory is complicated by the fact that, as a soft x-ray emitter, it requires special storage and handling. In particular, the requirement for heavy lead storage, or some combination of lead lining and storage outside of the space vehicle, would greatly limit its feasibility as a test substance under the conditions envisaged.

The use of carbon monoxide as a method of determining red blood cell volume dates back to the days of Haldane in 1900, although more recent applications have refined the process <sup>(278)</sup>. Whereas the radioisotope measure largely defines the volume of the circulating red cells, the CO method includes hemoglobin in bone marrow, muscles, and probably other extravascular pigments, and thereby overestimates the apparent red cell mass by about 12-16% <sup>(139)</sup>. The method requires introduction of a known amount of carbon monoxide into the blood by inhalation. The increase in CO content of the blood divided into the total amount of carbon monoxide administered gives the blood volume. The measure can be readily repeated, since the CO absorbed is effectively gone within a day. For the calculation, it is necessary to know the CO content of the blood before administration of CO, the CO content of the blood after administration of CO, the loss of CO, if any, during and after the period of administration, the CO content and volume of the inhaled air, and the amount of residual unabsorbed CO in the expired air. Full details of the technique and measurements are described in the paper by Root and his associates <sup>(278)</sup>, but essentially it calls for inhalation of air via an open system, with valving into a 100 liter Douglas bag, or equivalent. A known quantity of CO (about 240 ml) is introduced into the inlet line over a period of about 3-4 minutes. At the same time, collection of expired air is begun in the Douglas bag and is continued for a total of 10 minutes. An initial reference blood sample is taken before administration of CO, and four others are taken at 15 minute

intervals from the time of CO administration. The blood samples, and the bag air, are measured for CO content, using for example, a gas chromatograph. The volume of the bag air is also measured, by for example, an integrating flow meter, and the quantity of CO in the bag is calculated. Back extrapolation of the CO content of the blood samples to zero time and calculation of the total volume of CO absorbed allows calculation of the red cell volume.

It will be noted from the foregoing that the use of carbon monoxide in a manned space laboratory for the purposes of measuring red cell volume gives rise to considerable problems. In addition to the complexity and bulk of the apparatus, and the technical demands of the measurements, a major problem arises from the requirement to store, manipulate, and breathe a highly toxic gas within the confines of a sealed cabin. This alone must be considered a serious drawback to utilization of the technique. At the same time the only other feasible technique, namely, the use of Cr<sup>51</sup>, is also technically demanding and potentially hazardous.

Consideration, therefore, must be given to deriving a calculation of blood volume from a measure of plasma volume alone (e. g., by a dye technique). Theoretically the blood volume can be calculated from the plasma volume as follows:

$$BV = \frac{PV}{100-H} \times 100 \quad (78)$$

where BV = estimated blood volume

PV = measured plasma volume

H = corrected hematocrit.

The corrected hematocrit is the measured hematocrit of the sample corrected for the amount of plasma trapped in the packed cell column. The correction depends on the centrifugal force used and the duration of centrifugation. At 1500 rpm for 30 minutes the factor is 0.96<sup>(139)</sup>.

Still another factor requires consideration, namely, that the total body hematocrit is not necessarily the same as the hematocrit measured from a venous sample. Gregersen and Rawson<sup>(139)</sup> discuss this consideration, on the basis of much previous work, and point out that in man plasma-

hematocrit estimates of blood volume are consistently higher than cell-hematocrit estimates. Furthermore, comparison with measured blood volumes shows that the plasma-hematocrit method gives an overestimation which varies with the venous cell percentage, while the cell-hematocrit method underestimates blood volume by a constant amount. From this data, the ratio of overall cell percentage to venous cell percentage can be determined. This ratio gives the factor by which the venous cell percentage (venous hematocrit) must be corrected to compute the total body hematocrit, and is termed  $F_{\text{CELLS}}$ . Provided  $F_{\text{CELLS}}$  is a constant, the blood volume can be calculated from the plasma volume and the corrected hematocrit of the venous sample as follows:

$$BV = \frac{PV}{100 - (H \times F_{\text{CELLS}})} \times 100 \quad (79)$$

where BV = estimated blood volume

PV = measured plasma volume

H = corrected hematocrit of venous sample

$F_{\text{CELLS}}$  = correction factor for total body hematocrit

The value of  $F_{\text{CELLS}}$  in the normal healthy man is considered to be 0.91. It cannot be stated at this time, however, that this value remains constant in the conditions of altered hydration and fluid distribution that might be associated with prolonged space flight, and even under the best of circumstances the method has a high expected error.

### Body Cell Mass

As already noted, the concept of measurement of body cell mass depends upon the fact that all body cells contain potassium in a more or less constant concentration. The total potassium content of the human adult male is 50 to 54 mEq per kg of body weight (103) or 150 mEq per kg of cell water (228), or 68.1 mEq per kg of lean body mass (348), of which about 90% is intracellular, 90% of the latter being in muscle cells ( ). The total amount of potassium in the body is then a linear function of the body cell mass. Such a body cell mass includes all the cells of the body with their protoplasm and membrane, but without any interstitial fluid. Thus, a measure of total body potassium can provide a measure of the body cell mass.

To obtain such a value, however, requires a measure of either the 24 hour equilibrium distribution of the radioisotope  $K^{42}$ , or a whole body count of the naturally occurring isotope  $K^{40}$ . Measurement of  $K^{42}$  provides a value for the total exchangeable potassium, which represents about 98% of the total body potassium (228). The unmeasured fraction is the small slowly exchanging component of erythrocyte potassium, and possibly some slowly exchanging potassium in the central nervous system. As previously noted, the  $K_e$  in mEq multiplied by the factor of 8.33 yields the body cell mass in grams.

In the original technique by Corsa and his associates (68) in Moore's group, about 100 microcuries of  $K^{42}$  were given by intravenous injection as 10-30 ml of potassium carbonate solution in saline, with a concentration of 0.6 to 1.8 mEq per liter. Urine was collected over the next 40-60 hours and analyzed for radioactivity and potassium concentration. Heparinized blood samples were collected from some subjects between 20 and 40 hours after injection of  $K^{42}$ . Radioactivity was measured by geiger tube on aliquots of both the injected material and the samples, evaporated to dryness in 10 ml ashing dishes. Allowance was made for intrinsic counts in the dishes and for background. Overall coefficient of variation for the urine samples was about 2.5% and for the injected aliquots less than 1%. Blood samples were centrifuged to separate cells and plasma; protein free filtrates of each were analyzed for radioactivity and potassium. Potassium analyses for urine and blood were mostly done by chemical methods, although a few were measured by flame photometer.

Total exchangeable potassium was derived as follows:

$$K_e = \frac{K_i^{42} - K_o^{42}}{K_u^{42}/K_u^{39}} \quad (80)$$

- where  $K_e$  = exchangeable potassium (mEq)  
 $K_o^{42}$  = radio-K excreted in urine to time of equilibrium sample (units)  
 $K_u^{42}$  = concentration of radio-K in urine samples (units/L)  
 $K_u^{39}$  = concentration of chemical potassium (including  $K^{40}$  and  $K^{41}$ ) in urine samples (mEq/L)  
 $K_u^{42}/K_u^{39}$  = equilibrium urine specific activity (units/mEq)

With the evolution of the multiparameter approach developed by Moore's group, and described by McMurrey and his associates <sup>(218)</sup>, the  $K^{42}$  is injected in 50 ml of 0.85 saline as  $K^{42}CO_3$  in a dosage of 350 microcuries, along with  $Na^{24}$  also in 50 ml of saline. It is allowed to equilibrate for 24 hours, during which time urine and other drainages are collected. After 24 hours equilibration, a venous sample of 60-80 ml is taken. An appropriate reference standard of  $K^{42}$  is made at the time of initial injection, subsequently counted at the time of sample counting, and corrected to time zero. Serum is separated from the sample, and its potassium content concentrated 5 to 10 times by chemical reactions. The concentration of the concentrate is thereafter determined by flame photometry. A resuspended 2 ml aliquot is subsequently counted in a well-type scintillation counter. Urine and other outputs are handled in the same manner.

Since the samples also contain  $Na^{24}$  and  $Br^{82}$ , separation of the counts is required. By arranging dosages of  $Na^{24}$  and  $Br^{82}$  to give a suitable preponderance of  $Na^{24}$ , and counting the samples twice in the same detector at an interval of 24 hours, advantage is taken of the differential decay of the two materials.  $K^{42}$  specific activity is calculated from the counts of the concentrate and the actual concentration of the concentrate. The  $K_e$  in turn, is determined by dividing the difference between the counts injected and the counts excreted by the specific activity. Full details of the procedure and calculations are presented in McMurrey's paper <sup>(218)</sup>. Various other groups have described allied techniques <sup>(38, 242)</sup>.

In any event, it has to be borne in mind that, in addition to the complexities imposed by handling and counting problems, the usefulness of  $K^{42}$  or other short lived radioisotopes of potassium as a measure in a manned space vehicle is virtually nullified by the length of the half-life, which in the case of  $K^{42}$  is about  $12\frac{1}{2}$  hours. Thus, without resupply, it would be possible to obtain only one measure after launch, and even resupply would be difficult within the time available. One cannot, of course, dismiss the possibility of making radioisotopes within a nuclear propulsion unit.

The alternative of making total body counts of the low-energy naturally occurring radioisotope  $K^{40}$  is even less hopeful under the circumstances. Two methods are used for whole-body potassium counting. One method

(225) involves placement of the subject within a shielded chamber, with walls of lead and steel, and measurement of the emitted gamma from the whole-body  $K^{40}$  by suitable placement of a large (4") NaI (TI) crystal as a detector, along with a pulse height analyzer and supporting electronics. The most appropriate scanning geometry is obtained with the subject reclining in a special tilting chair and the crystal mounted over the chest-abdominal region. The total weight of body potassium can be derived from the counts per minute of  $K^{40}$  by correcting for the variation in geometry and applying a factor representing the counts per minute of a known amount of potassium. Details of the procedure and calculations are given in the paper of Miller and Remenchik (225).

The second method (14) involves placement of the subject within a double-walled cylinder 18" in diameter and 72" in length, the inside wall of which is completely surrounded by liquid scintillation solution. Geometrical efficiency is nearly 100% and counting efficiency varies little with the position of the subject. The Los Alamos machine has several energy channels and is usually set for  $Cs^{137}$  and  $K^{40}$ . Its operation is programmed by a computer, and other nuclides can be examined. Calibration is undertaken daily, using standard weight phantoms containing KCl, or sometimes control subjects given  $K^{42}$ . The duration of a routine count is 200 seconds.

It is very apparent that neither of these methods of whole-body counting is applicable to the conditions of a manned space laboratory. Thus, it would seem that there is no way of obtaining a direct measure, either with exchangeable potassium or whole-body potassium, to represent the body cell mass. Since most of the potassium is, however, contained in the muscle mass, some other index of muscle metabolism suggests itself.

A close relationship has been shown between total exchangeable potassium and creatinine, and of course, as already noted, with body cell mass. Corsa and his associates (68), in their original work with  $K^{42}$ , found in five healthy male subjects a direct association between the exchangeable potassium and the 24 hour urinary excretion of creatinine, with a correlation coefficient 0.98. A similar association, with a coefficient of 0.90 to 0.91 was found by Muldowney and his group (230) in

Glasgow, in spite of the fact that the creatinine measures in this series were derived from single specimens of urine at the 24 hour mark, and dietary protein intake was not controlled.

Creatinine is the anhydride of creatine, which is a normal body constituent with about 120 gm being contained in the normal adult human body (286). Of this, 98% is contained in the muscles, mostly in the form of creatine phosphate. As an energy storage system creatine phosphate is formed by the reaction of creatine with adenosine triphosphate. Isotope experiments have shown that creatine is formed from the three amino acids arginine, glycine, and methionine, and is found in the blood in the range of 2-8 mg per 100 ml. Creatine phosphate is metabolically degraded in muscle tissue, with formation of creatinine. The latter is found in the blood in the range of 1 mg per 100 ml and is excreted in the urine. Creatine is not a normal urinary constituent in men although it may be found normally in children and in women. Excretion of creatine in the urine may be found under certain clinical conditions such as diabetes, exophthalmic goiter, fevers, muscular dystrophies, and starvation. In fact, it tends to be found in those conditions where there is an increase in the normal catabolism of muscular tissue, although it may also be found where a high protein diet is being consumed. Increase in creatinine excretion has also been observed in animals (rats, dogs, and monkeys) following exposure to high dosages (1000 - 1500 rep) of ionizing radiation (17, 177,343).

The daily output of creatinine in the urine tends to be constant for the normal individual, amounting to 1.5 to 2 gm for men. When expressed as a coefficient, namely, mg creatinine excreted per day per kg of body weight, the output can be used as an index of the body cell mass, particularly the muscular portion, and has a value of about 20 to 26 in men. The value depends upon the muscular development of the individual and would be even more useful if expressed in terms of the lean body mass. Since creatine and creatinine are in equilibrium, the ratio of blood creatine to blood creatinine is also a useful index of the state of the muscle mass.

It is obvious of course that measures of either creatinine or creatine do not provide any actual measure of the body cell mass. This can be achieved very indirectly, however, by relating the value of the measured creatinine in the urine to the total exchangeable potassium, and in turn deriving a value for the body cell mass. Muldowney and his associates (230), on the basis of single measures of urinary creatinine in 16 men and 14 women developed a regression equation linking the two, namely:

$$K_e = 1.36C + 745.6 \quad (81)$$

where  $K_e$  = exchangeable potassium (mEq)

$C$  = creatinine excretion (mg/day)

While application of this equation to another group of subjects would not be reasonable, there is a good probability that appropriate regression equations for members of the astronaut population could be developed in ground-based experiments and thereafter be applied in operational conditions.

Techniques of accurate measurement of creatinine and creatine are complex. The Folin-Wu method, however, which is not entirely specific, would be feasible with a colorimeter. Details are described in standard clinical laboratory texts. In essence, the creatinine is determined from the red color developed in the reaction that takes place with alkaline picrate in a protein-free filtrate. Creatine is determined similarly, after first being converted to creatinine.

From the various measures and calculations described above, the relationships of the body cell mass and its supporting structures can be determined. The thiocyanate space provides a measure of the plasma and interstitial-lymph volume. Subtraction of the measured plasma volume provides a value for the interstitial-lymph volume. The transcellular volume is given by the difference between the measured total body water and the thiocyanate space. Blood volume is derived from the plasma volume, either by calculation from the hematocrit or by addition of the red cell mass; and body cell mass is obtained either from measurement of body potassium or calculation from creatinine. Intercellular water is derived from the difference between the total body water and the extracellular water. The fat-free body is calculated from the body weight

less the body fat, while the fat-free solids are represented by the fat-free body minus the total body water. Finally the dry, fat-free, bone weight can be estimated by calculation, or by nomogram, from the  $K_e/FFS$  ratio.

The major weakness in applying the system to subjects within a manned space laboratory lies in the inability to obtain a satisfactory measure of exchangeable potassium. This fact would seem to be one of the few reasons for considering a space-borne radioisotope laboratory.

Even without radioisotopes, however, some of the handling and processing procedures for chemical testing will be difficult in the weightless environment. Wet chemical methods in particular will be difficult to handle. It is obvious that each test procedure finally selected for use in space will have to be carefully examined and performed by knowledgeable technologists on the ground to determine the actual problems involved in conducting it, in preparing standards, or utilizing pre-prepared standards, in dissolving solid chemicals and mixing liquid solutions, and in preparing final samples for instrumental evaluation. Conceptual designs for integrated test consoles have already been developed which would satisfy most, if not all, testing requirements, but it is necessary for actual tests to be conducted in a suitable simulator to determine the efficacy of the selected procedures and equipment. It would seem to be necessary, in fact, to determine the feasibility of conducting certain types of laboratory operation under conditions of simulated weightlessness, and to conduct representative operations in actual space flight, before utilizing similar procedures in manned orbiting laboratory.

As a further note, the work of Weber and his associates (335) requires comment. While the chemical analyses suggested in the current study are normally carried out on blood or urine, it is possible that future development may indicate that parotid secretion would be an acceptable substitute at least for some analyses.

## Recommendations

Examination of the requirements for body measurement indicates that elements of both the somatolytic and multiparameter approaches can be employed to provide feasible and useful information in a manned space laboratory. Any final recommendations, however, both as to procedure and equipment, must be subject to a systems engineering analysis and actual operational test in orbital space flight.

The somatolytic approach involves considerations of body density, dimensions, and water content. Measurements in each of these areas can provide significant information. Various attempts have been made to quantify body composition in terms of fat content, lean body mass, and body water. It has been shown that water content varies with the fatness of the individual in health and disease, and that the water content of adipose tissue will vary with changing conditions. Consequently simple relationships do not always apply. The most generally acceptable relationship is found in the equation of Siri's ( 306 ) which treats total body water and density as independent variables and provides a calculation for fat content with potential error of  $\pm 2\%$ .

Calculation of body density is not feasible in a space laboratory by the conventional means of underwater weighing, and must be made from independent determinations of body weight and volume. Consideration of various techniques for measuring body weight suggests three methods which would appear to have the most potential in weightless conditions, namely, the use of a spring-mass system, a linear acceleration system, and a centrifuge. The most development has taken place with the spring-mass system which in ground-based conditions has demonstrated an accuracy in body weight measures to within 1/2 lb. Less developmental work has taken place with the other two systems, but a centrifuge in particular, if carried for other reasons, shows promise as a tool for determining body mass. It must be borne in mind that the constants used in ground-based mechanical systems, particularly in the spring-mass oscillating device, are not necessarily the same as those required under weightless conditions. Any such system will have to be revalidated in the weightless state. The possibility of determining weight (mass) as a function of capacitance, by inserting a mass between the plates of a capacitor, might also be considered. At this time it is

difficult to recommend one system strongly over another. Development might well be encouraged in all areas until hardware can be tested operationally.

From many points of view accurate determination of body volume offers difficulties as great as those for body mass. A chart is presented (Figure 16) from which an estimate of body volume can be made from weight and height, with an error of up to 3.5%. The possibilities of photography (stereophotogrammetry and monogrammetry) must be borne in mind, but while the error is less ( $\pm 2\%$ ) than with the chart, the techniques would require considerable development for use in space. Complex, but highly accurate techniques (within the recommended tolerability of  $\pm 0.1$  liter) utilizing gas dilution principles, or air displacement principles, could be modified for space use. The gas dilution system, which provides highly accurate measures, calls for a special chamber with complex plumbing and ventilation, a helium source and injection system, a helium dilution capability, and critical regulation. The air displacement system also calls for a special chamber with ventilation and critical regulation, but no extra gas manipulation is required. It would seem that modification of the whole-body plethysmograph recommended in the Respiratory Section as part of a modified airlock would better meet the requirements for this purpose. The possibilities of developing suitable photographic and capacitance techniques should, however, be kept in mind.

The determination of changing body dimensions using somatometric techniques is readily undertaken with relative simplicity in orbital conditions. Multitudinous measures have been made and have led to the development of numerous regression equations showing high correlations, but sometimes not too meaningful in content. Bearing in mind the requirements of feasibility and simplicity within the confines of an orbiting space laboratory, but seeking at the same time a maximum of useful information, the minimum battery of measures would seem to include the 11 circumferences utilized by Behnke (30), (Table 8), which in turn include those measures used by Steinkamp et al., (314, 315) in developing their valuable regression equations, along with measures of triceps, subscapular and thoracic skinfolds as made by a standardized caliper. Skinfold measures act as fat indices and allow calculation of various useful regression equations.

Radiographic techniques have been found valuable in ground-based studies, both in soft tissue estimations and in determining bone calcium content and distribution. While x-ray facilities may well be available in an orbiting space laboratory, it is doubtful if their usefulness in this field would justify the requirement for the additional bulky and sophisticated equipment that would be necessary for on-board evaluations of this kind. It is possible, however, that the output of a photoscanner might be employed to telemeter information to ground, from which estimations might be made. Considerable development, however, would be required before such a technique could be recommended.

Ultrasonic devices have also been used in the determination of body composition. While the techniques would appear to be valid, they would seem to hold no advantage over other simpler approaches. The same reservation applies to the determination of body fat content by inert gas absorption.

The multiparameter concept in the evaluation of body composition is concerned with the nature of the body cell mass and its relationships to supporting structures and body fluids. Implementation entails determination of body fluid compartments, cellular masses, and cell mass constituents, from which the cell masses can be calculated. The measures to be made include total body water and its subdivisions, total exchangeable potassium, total exchangeable sodium, total exchangeable chloride (and their equivalents), plasma volume, red cell mass, and body weight.

In summarizing the requirements of the multiparameter concepts of determining body composition, it is emphasized that in terrestrial conditions, with adequate analytical and radioisotope laboratory facilities and supplies, methods employing radioactive tracers or some type of tagging are inherently more accurate and sometimes simpler than chemical methods of estimating sundry volumes and spaces. In a manned space laboratory, the shielding and handling requirements of both apparatus and supplies, and the difficulties in some cases of retaining isotopes with enough activity to be useful for more than a few hours or days, make the justification of radioisotope procedures somewhat doubtful, particularly where other methods can be usefully employed. There is no doubt that it is within the state of the art to design a suitably shielded scintillation counting device with exchangeable counting detectors for beta, gamma,

and x-ray emissions, and to devise suitable shielding for test materials. Resupply, or on-board manufacture, of short-lived isotopes could also be considered. The only situations, however, where radioisotopes might be deemed the prime method of accurate measurement are found in the estimation of red cell mass ( $\text{Cr}^{51}$ ) and the estimation of exchangeable potassium ( $\text{K}^{42}$ ). The last named measure is of great significance, but nevertheless it is difficult to justify a radioisotope laboratory on the basis of one measure, when in fact it would contribute little in other areas that could not be achieved by other means.

For the estimation of total body water there is little doubt that the use of deuterium oxide as a tracer is the most accurate and feasible method, provided a mass spectrometer is available for measurement of samples. At the same time this technique calls for some complex processing to prepare the sample for counting. Consequently it is suggested that consideration might be given to a technique utilizing alcohol absorption. Further validation and comparison with accepted methods is, however, required before a final recommendation could be made.

For extracellular fluid spaces the use of radioisotopes is not recommended for the reasons noted above. Thiosulfate and thiocyanate each offer a potential alternative. Because of its greater simplicity in technical execution, however, it would appear that the use of thiocyanate has more to recommend it than has thiosulfate.

With respect to plasma volume estimation there is little doubt that the method of choice lies with the use of the diazo dye T-1824, or some equivalent, despite the requirement in estimation for a spectrophotometer, preferably of the dual beam variety. A spectrophotometer, however, will have multiple uses in a manned space laboratory. The use of radioisotopes in plasma volume measurement has no advantage to offer for space-borne use.

Measurement of blood cell volume, as noted above, presents great difficulty. The only techniques developed have employed radioisotopes, or carbon monoxide. The accepted isotope,  $\text{Cr}^{51}$ , is a soft x-ray emitter which requires special handling and storage. Should a radioisotope facility be deemed advisable on board

a manned space laboratory there is no doubt that use of  $\text{Cr}^{51}$  would be the method of choice. Failing that, and considering the use of CO as an unacceptable toxic hazard, the only alternative is to employ a calculation, such as that described, using the measured plasma volume and a value for the corrected whole-body hematocrit. It is again noted here that the correction factors utilized in normal healthy man in terrestrial conditions may not be applicable in the orbiting laboratory where changes may be found both in blood cells and in fluid distribution.

To obtain a measure of body cell mass is even more difficult. The measurement of whole-body  $\text{K}^{40}$  demands a bulk and weight of screening and apparatus that will be entirely unacceptable in the foreseeable future, while measurement of exchangeable potassium with  $\text{K}^{42}$  not only requires facilities of a radioisotope laboratory but employs an isotope with a half-life that would barely allow one measurement. The somewhat weak alternative suggested calls for measurements of the circulating and excreted creatine and creatinine as an index of muscle catabolism. As also suggested, it would seem possible on the basis of premission ground-based experiments to develop regression equations linking the excreted creatinine level with body potassium and in turn relating the latter to body cell mass.

With suitable combination of the above measures, however, data can be obtained to define, within a space laboratory, the body composition and any dynamic changes in size, density, lean body mass, cell mass structure, skeletal structure, fat content, intracellular and extracellular fluid (including the blood volume and components), and fluid distribution, that may take place as a result of or in association with prolonged space flight.

In considering the foregoing discussion on certain cardiovascular, respiratory, and anthropometric techniques of physiological measurement, it is again emphasized as has been intended throughout the text, that the analysis made here is the result of a theoretical study. The recommendations which have been made are those which

appear to be the most suitable for consideration; those techniques which have been rejected are those which have been found manifestly impracticable by reason of skill demands, complexity, bulk, and weight of apparatus, unsuitability for a gravity-free confined chamber, potential hazard, or the requirement for undue violation of the subject. But all techniques recommended require comprehensive testing for feasibility and effectiveness, and experience within the simulated and real spacecraft environment. Many suggested measurement methods require in addition, considerable development in instrumentation and method, and further validation before acceptance. It is also apparent that comprehensive consideration will need to be given to the development of integrated instrumentation, time-optimizing protocol of measures, and streamlined procedures in order to make the most economical use of time, skill, weight, and volume, and obtain the maximum information possible within the constraints of the system.

-END-

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