DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE Hardin B. Jones
Committees, Speeches, Reprints, Papers
BANCROFT/UARC ID NO.
79/11-2c
COPY
CARTON NO.
3
FOLDER NAME Reprints Relationship of Age and Sex to Early Mixing of Na24 in Normal Man
NOTES
p 1/7
FOUND BY/DATE FOUND
Susan Storch 11/15/84

722171

Reprinted from JOURNAL OF APPLIED PHYSIOLOGY
Vol. 8, No. 5, March, 1956
Printed in U.S.A.

BEST COPY AVAILABLE

Relationship of Age and Sex to Early Mixing of Na^{24} in Normal Man[1]

ENRIQUE STRAJMAN, HARDIN B. JONES, PAUL J. ELMLINGER, JOHN W. GOFMAN AND GERTRUDE E. WARD. *From the Donner Laboratory of Medical Physics, Division of Medical Physics, University of California, Berkeley, California*

THE RATE at which various gases are eliminated from the human body has been shown to be slowed by the aging process (1-3). The processes of diffusion and blood circulation are important controling factors of the rate of gas elimination through the lungs. Since diffusion seems to be very rapid and with similar rate constants for various gases (2), the limiting factor in the rate of elimination has been assumed to be the blood perfusion of the body constituent tissues (2).

In previous human studies (4) with $Na^{24}Cl$ it was observed that an early component of sodium movement was much faster in younger than in older men. The early component observed subsequent to a single intravenous injection of Na^{24} is of the same order of magnitude as one of the rates of blood mixing. Since the blood-mixing process is closely related to blood circulation, it was thought that these measurements could provide a better method of determining the relationship of blood circulation to aging.

The individual variations observed in normal subjects of the same age suggested that these measurements might also be useful as a test for determining the physiological age vs. the chronological age of human beings, using as an aging criterion the effect on blood circulation.

The aim of the present work was to measure an early rate of Na^{24} movement on a larger number of normal humans of both sexes to evaluate such variables as regression slope of an early mixing rate with age, the correlation coefficient between these two variables for a large part of the life span, the existence of any sex difference, the individual variations and the error of measurements. The knowledge of these variables is considered important not only for judging these measurements as a test of physiological age and the aging process but also for studying the effect that physical, chemical and pathological factors might have on the dynamics of molecular transportation in humans.

Received for publication March 14, 1955.
[1] This work was supported in part by the National Heart Institute, National Institutes of Health, and in part by United States Atomic Energy Commission.

METHODS

Subjects. The subjects in these studies were normal men and women from 22 to 90 years of age who volunteered for the measurements. They were apparently in good health with no past history of serious diseases. They were working or retired persons whose living and working conditions indicated that they were a sample of the average population. Sixty-three men and 70 women with ages evenly distributed within the age range chosen were studied. There were approximately five subjects in each 5-year class interval of the span of age.

Technique. Subjects rested in the supine position for at least 15 minutes before injection. An isotonic solution of 30-50 μc of $Na^{24}Cl$ was then injected in a few seconds into an arm vein. A scintillation counter completely shielded with about a 2-inch thickness of lead and a frontal aperture of $\frac{7}{8}$ inch was placed over the precordial region, about 5 cm from the mid-line at the fourth intercostal space. The scintillation counter was connected to a scaler and a recording device which plotted the accumulated counts for each 24-second interval. These counts were expressed on the record as the counting rate per minute. Measurements were continued from a minimum of 35 minutes in a few cases to 2 hours in others.

Analysis of Data. The concentration of radiosodium measured over the heart region, following the intravenous injection of $Na^{24}Cl$, increases very rapidly to a maximum 15-30 seconds after administration. It is followed by a fast decrease during the first minutes, continuing with a slower disappearance thereafter.

From previous analyses of Na^{24} time-concentration curves in normal human beings (4) at least six components were determined by using the regular graphic method of estimating exponential functions. Of these components, the one designated as the second was considered of particular interest in the present studies.

The second component is practically resolved within the first 90 seconds to 10 minutes in adults. Therefore, in most curves from measurements continued from 35

1161224

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE
Harvard Jones Committee . . . Papers
BANCROFT/UARC ID NO.
79/11-2c
COPY
CARTON NO.
3
FOLDER NAME
Early Mixing of Na^{24} in Normal Men
NOTES
p 317
FOUND BY/DATE FOUND
Jessica Storch 11/15/94

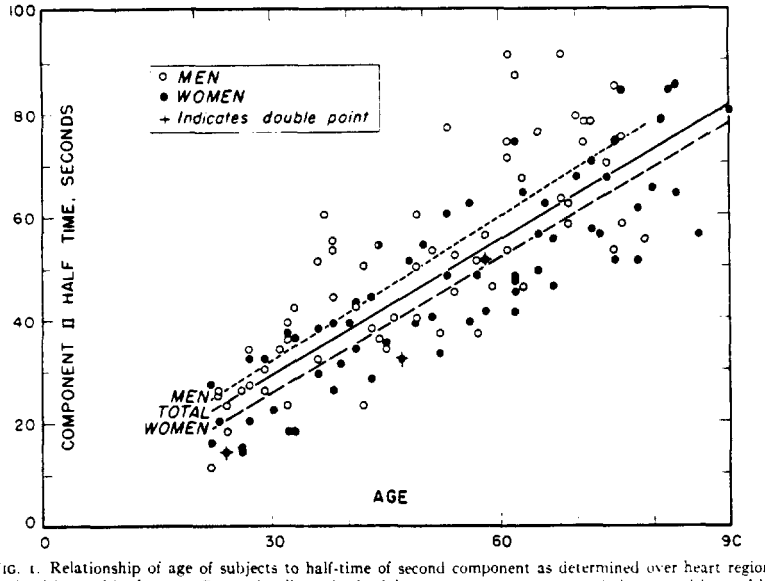

FIG. 1. Relationship of age of subjects to half-time of second component as determined over heart region of normal subjects of both sexes. Regression lines obtained from 63 men, 70 women and the 133 subjects of both sexes.

minutes to 2 hours, the first three components, plus the largest part of the fourth, are included. Estimations of the fifth and sixth components were not possible in the present curves because of the short time of measurement. Consequently, approximate values of the fifth and sixth components had to be calculated. The hypothetical fifth component was drawn on semilogarithmic paper beneath the actual curve as an almost horizontal line for the first 35 minutes. For the fifth component the amplitude at zero time was assumed to be 10% of the concentration of the curve up to the fourth component, the rate having a half-time of over 1 hour. These were approximate values obtained from previous longer measurements with sodium. The hypothetical fifth component line was then subtracted from the actual curve and the fourth, third and second components were extracted following the regular graphic *method for estimating exponential functions*. Because of the slowness of the fifth and sixth components in relation to the second, plus the small amplitude of the fifth, the use of an average value as a correction factor to subtract the effect of these slow components adds only a negligible error to the estimation of the second component.

When measurements are continued for at least 60 minutes a simpler procedure for estimating the rate of the second component can be followed by extrapolating either the fourth or the fifth components from the actual curve to zero time. The subsequent extraction of the earlier components will result in a half-time of the second component with slightly larger error than with the method previously described.

The second component is expressed in terms of half-time in seconds instead of the constant K because of the more common usage of this value.

Statistical Analysis. The correlation chosen to be analyzed was *a) between the half-time of the second* component and the age of the subject and *b)* between the values of two half-times obtained by either separate measurements on the same subject or two evaluations of the same measurement. For that purpose, in both cases the method of least squares was used to determine the regression and correlation coefficients and the standard error of estimate.

RESULTS

The analysis of the curves from the group of subjects studied indicates that the second component develops during the first 1.5 minutes for the faster rate subjects and during 10 minutes for the slowest; the half-time ranged from 31 to 91 seconds. The half-time of the second component was plotted against the age of the subjects as shown in figure 1. Although a wide scattering and overlapping is observed for the individual points of men and women, the general trend is for the rates to be slowed

1161225

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE
Harlan B. Jones Committee Papers
BANCROFT/UARC ID NO.
79/112c
COPY
CARTON NO.
3
FOLDER NAME
Early Mixing of Na in Normal Men
NOTES
p 317
FOUND BY/DATE FOUND
Susan Steck 11/15/94

with aging of the subjects. In general, faster rates were observed in women than in men of the same age, as shown in the regression lines of both sexes. The regression line was assumed to be a straight line. The error of individual measurements is too large and the number of subjects too small to prove whether there is a nonlinear regression.

The results and statistical analysis of this group are also shown in table 1. As may be observed, the average half-time for the second component in men was 50.5 seconds for an average age of 49.8 years, whereas in women it was 45.6 seconds for an average age of 53.1 years. The regression coefficient, b_{ha}, was for men 0.93 ± 0.06 sec yr., for women 0.86 ± 0.03 sec yr. and for the group of both sexes 0.87 ± 0.04 sec yr. The standard error of estimate, σ_{ha}, was 11.9 seconds for men, 8.8 seconds for women and 11.1 seconds for the group including both sexes. The correlation coefficient, r_{ha}, was 0.79 for men, 0.88 for women and 0.65 for both sexes together.

To estimate the difference between the second component half-time of both sexes, 50 years was chosen as the age for comparison, since the average age of both groups was different. The half-time corresponding to 50 years estimated from the regression line is 50.7 seconds for men and 42.9 seconds for women, or a difference of 7.8 seconds (table 2).

To determine the possibility of the results being influenced by knowing the age and sex of the subjects, the time-concentration curves of 18 men and 19 women from 30 to 50 years of age were replotted, coded and shuffled to be estimated again by the same person without knowledge of the age and sex of the individual. In addition, nine curves taken at random from the same group of subjects were duplicated and mixed with the others. This group of subjects, hereinafter referred to as the unknown group, was compared to the same subjects, hereinafter referred to as the known group, which had previously been estimated with knowledge of their age and sex.

The results between these known and unknown evaluations are presented, part in table 2 to compare the sex difference, and part in table 3 to compare the regression and correlation coefficients of the half-time with age and the standard error of estimate.

TABLE 1. RELATIONSHIP OF AGE TO RATE OF SECOND COMPONENT

Subj	No.	Av. Age yr.	$T\frac{1}{2}$ sec	σ_{ha} sec	b_{ha} sec/yr	r_{ha}
Men	63	49.8	50.5	11.9	0.93±0.06	.79
Women	70	53.1	45.6	8.8	0.86±0.03	.88
Mixed	133	51.5	47.6	11.1	0.87±0.04	.65

Average half-time $T\frac{1}{2}$ of second component. Regression coefficient b_{ha} standard error of estimate σ_{ha} and correlation coefficient r_{ha} of half-time with age in group of 133 normal subjects of both sexes.

The reliability of two tests was estimated by measuring 20 subjects twice on different days and each measurement was estimated only once. The average half-time was 47.6 seconds for the first measurement and 45.4 seconds for the second measurement. The standard error of estimate, σ_{tt}, was 8.4 seconds and the correlation coefficient, r_{tt}, between both tests was 0.81.

The reliability of two separate evaluations of the same measurements was determined by comparing the estimation of 37 known subjects with the estimation of the same subjects from unknown curves. The average half-time was 39.0 seconds for the first evaluation and 38.8 seconds for the second. The standard error of estimate, σ_{tt}, was 8.0 seconds and the correlation coefficient, r_{tt}, between both evaluations was 0.75.

In a group of nine unknown subjects where two evaluations from the same curve were made, the average half-time for the first evaluation was 39.6 seconds and 40.8 seconds for the second. The standard error of the estimate, σ_{tt}, was 6.4 seconds with a correlation coefficient, r_{tt}, between both evaluations of 0.88.

The average of two measurements of the same individual with one evaluation each, gave an r_{ha} of 0.77 and a σ_{ha} of 8.7 seconds, whereas for the average of two evaluations of the same curve r_{ha} was 0.58 and σ_{ha} was 8.6 seconds.

Since measurements were performed at various times, the data were divided into subgroups of morning and afternoon, and regression lines were estimated in both sexes, in order to determine whether there was any difference. For both groups, as shown in figure

116122b

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE
Hardin B. Jones Committees ... Papers
BANCROFT/UARC ID NO.
79/112c
COPY
CARTON NO.
3
FOLDER NAME
Early Mixing of Na24 in Normal Man
NOTES
p. 4/7
FOUND BY/DATE FOUND
Susan Storch 11/15/94

TABLE 2. STATISTICAL SIGNIFICANCE OF SEX DIFFERENCE OBSERVED IN HALF-TIME OF SECOND COMPONENT

Subj.	Age Level	T ½ sec M	T ½ sec W	t Ratio	Probability
Known, 133	50	50.7	42.9	3.84	0.01-0.001
Known, 37	40	42.6	35.7	2.55	0.02-0.01
Unknown, 37	40	42.2	35.6	2.00	0.06-0.05

First group, 63 men and 70 women whose age and sex were known. Second and third group formed by same 18 men and 19 women, 30–50 yr. old, evaluated with knowledge of their age and sex in first group, and from unknown curves in the second. The t ratio and probability for each group.

2, the regression lines indicate faster half-times in the morning than in the afternoon in women aged from 22 to 55 years, in men aged from 22 to 65 years and slightly the opposite in the later years for both men and women. The regression slope was increased per year of life in the morning group to 1.02 ± 0.14 seconds in men and 0.94 ± 0.10 seconds in women, and in the afternoon group to 0.84 ± 0.06 seconds in men and 0.82 ± 0.09 seconds in women. However, the number of subjects studied was too small to give statistical significance to this difference.

DISCUSSION

From the various components previously observed in the sodium concentration curves (4), the second component was selected because it shows a marked association with the aging process and is more accurately estimated in a shorter time than the other components.

The correlation coefficient between the age of the subject and the rate of the second component was quite high and can be considered statistically significant. The correlation coefficient was further improved when each sex was estimated in a separate group.

The significance of these results is somewhat limited by the fact that the age and sex of the subjects were known to the investigator who analyzed the data. Therefore, it was thought necessary to estimate again some of the same subjects whose age and sex would be unknown to the person estimating it. In general, the results of this control evaluation show very slight differences between both estimations. The standard error of estimate, which indicates the data spread, was larger for the unknown group of men and women than for the known group by 1.8 seconds. This can be interpreted as a very small influence in knowing the age and sex of the subject. However, the differences obtained in both calculations are too small to change the significance of the age and sex relationship observed in the large group of known subjects.

The correlation between age and rate of the second component was more significant in the group of 133 subjects than in the group of 37 subjects, being in the known group slightly better than in the unknown. This difference of better correlation for the large group could be explained in part by the fact that the age of the subjects ranged from 22 to 90 years, whereas in the small group of 37, the ages ranged from 30 to 50 years.

The sex difference observed in all groups was quite marked, as summarized in table 2. In the large group of 133 where the sex was known, the difference was statistically very significant. The probability that the sex difference in that group is due to sampling is of the order of less than 1% with a t ratio of 3.84. In the small group of 37 where the sex was known, the same probability is between 1% and 2% with a t ratio of 2.55. In the same small group of subjects where the sex was unknown, the probability is between 5% to 6% with a t ratio of 2.00. The sex difference in the latter group should be statistically considered as only fairly significant. The decrease in significance of the small group might be explained as due to the smaller number of subjects, and also that the average age was 40 years instead of 50 years for the larger group, and the sex difference seems to increase with age.

The differences observed in the regression coefficient b_{ha} in men and women, which could also be expressed as representing the aging rate of their circulatory system, are statistically less significant than the sex difference observed in the average half-time for the same subjects. The difference in the regression coefficients in both sexes gave a t ratio of 1.81 with a probability of 0.10 to 0.05.

Sex differences have been found in dynamic

1161227

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE
Harrison B. Jones Collection — Papers
BANCROFT/UARC ID NO.
79/112c
COPY
CARTON NO.
3
FOLDER NAME
Early Mixing of Na^{24} in Normal Man
NOTES
p 517
FOUND BY/DATE FOUND
Susan Stark 11/15/94

studies of gases in humans. The rate of carbon monoxide elimination at rest was found to be faster in women than in men of approximate age (5). This sex difference was approximately maintained when the CO elimination rate was accelerated by exposure to an ambient pO_2 from 0.2 to 2.5 atmospheres. The oxygen recovery rate after mild exercise was found to be slower in a group of women than in men (6), although the oxygen recovery rate has been shown to be influenced by the aging of the subjects (1). Differences in physical fitness in both sexes might explain this reverse situation. The blood velocity rate has been determined as slightly faster in women than in men (7). The standard error of estimate σ_{b_a} from the regression line is a good index to estimate the significance of differences from normal behavior that might be observed in one or more measurements. For a single measurement, the standard error is quite large; it can be decreased by separation of sex, morning and afternoon measurements, as well as by two independent evaluations of the same curve. The average of two measurements on the same individual on different days also decreases the standard error.

The four main sources of variations contributing to the standard deviation are: *a*) the technical errors, *b*) the error in the graphic evaluation of exponential functions, *c*) the individual variations and *d*) the physiological variations. The number of cases analyzed is not large enough to evaluate all these individual variables statistically. However, it seems that the method used for estimating the exponential functions is the largest source of individual error. Apparently the individual differences and physiological variations under similar conditions of measurement are not very large and the effect of the aging process in itself seems to be the most outstanding phenomenon of these observations.

Interpretation of the Second Component. Substances introduced into the blood stream are transported within the blood and sometimes to other compartments following several rates of movements. The interrelation between the rates determined from the experimental data and the rates of mixing and penetration in the various compartments are not well established as yet, and are to be discussed in more detail elsewhere (8). It can be stated here, however, that the mixing of a substance within the blood after the intravenous administration of a single dose occurs primarily following three components.

TABLE 3. COMPARISON BETWEEN TWO SEPARATE EVALUATIONS FROM SAME CURVES OF SAME SUBJECTS

$b_{T_{1/2}}$ vs. Age			$\sigma_{T_{1/2}}$ vs. Age			$r_{T_{1/2}}$		
M	W	Mixed	M	W	Mixed	M	W	Mixed
Known subjects								
0.72	1.12	0.91	8.2	7.8	8.7	.46	.66	.55
Unknown subjects								
0.77	1.16	0.96	9.8	9.7	10.5	.45	.60	.48

First evaluation, labeled as 'known,' is from subjects whose age and sex were known. Second evaluation of same subjects from plotted curves with no clue to subject's age and sex is labeled as 'unknown.' Regression coefficient $b_{T_{1/2}}$ of half-time $T_{\frac{1}{2}}$ of second component with age, standard error of estimate σ, and correlation coefficient r, of group formed by 18 men and 19 women, 30–50 yr. old.

The first component represents the mixing of the injected substance within the lung pool and distribution to all the other body pools through the arterial tree. The second component probably represents the contribution to the mixing by the pools of high perfusion rate and situated close to the heart. The third component would represent the contribution to the molecular mixing by the pools of low perfusion rate and situated farther from the heart.

The rate of the second component, as measured after the sodium administration, seems to be of the same order of magnitude as similar early components observed after the intravenous administration of substances nondiffusible into the interstitial fluid (9). The diffusion of Na^{24} into the interstitial fluid through the capillary walls apparently does not modify the rate of movement of the second component. The second component in the sodium measurements is interpreted here as one of the rates which develops during the blood mixing.

What mechanism during the aging process might be responsible for producing such marked slowness of the rate of the second component is an interesting question to be elucidated. The possibility that capillary permeability to sodium might decrease during the aging process is difficult to prove. The present knowledge of dynamics of substances non-

1161228

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE
Harvey B. Jones Committee ... Papers
BANCROFT/UARC ID NO.
71/112c
COPY
CARTON NO.
3
FOLDER NAME
Early Mixing of Na 24 in Normal Man
NOTES
p 6/7
FOUND BY/DATE FOUND
Susan Stark 11/15/94

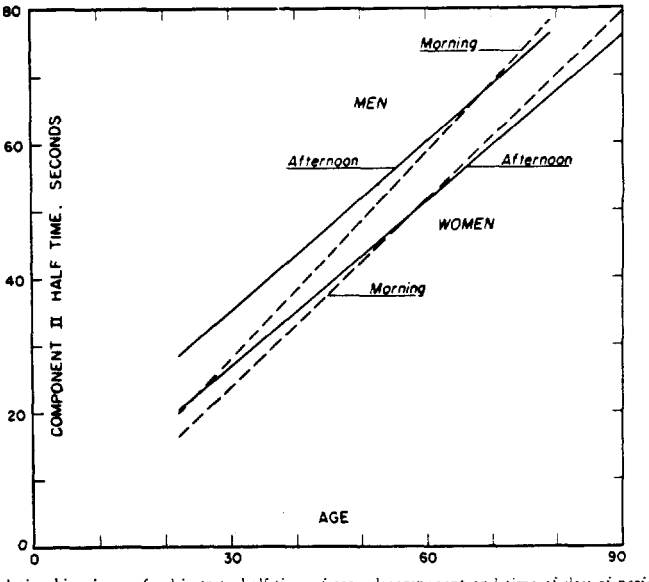

FIG. 2. Relationship of age of subjects to half-time of second component and time of day of performance of measurement. Regression lines obtained from groups of normal individuals. Men, 20 in morning and 37 in afternoon; women, 24 in morning and 46 in afternoon.

diffusible into the interstitial fluid (9) shows slight differences with no statistical significance. The hypothesis of a decrease in capillary permeability with aging has been controversial. The results obtained by Holman (10) in dogs using large molecules like proteins do not agree with a previous suggestion of a decrease in permeability by Drinker (11). The less restricted diffusion through the capillary wall for sodium chloride than for nonelectrolyte molecules, as shown by Pappenheimer *et al.* (12), decreases the probability that aging may influence the permeability of capillaries to sodium.

If capillary permeability is not an important factor in slowing the second component, the effect of aging in the cardiovascular system and consequently in hemodynamics should then be assumed to be the most important factor. Among the anatomical and physiological changes in the cardiovascular system observed during the aging process should be mentioned a decrease in cardiac output (13), an increase in the sclerosis of the arteries, peripheral resistance, blood pressure and blood viscosity and an acceleration in the pulse wave. The blood flow of certain organs, such as the kidneys (14) and muscles (2) has been reported to decrease markedly with age. Of all the factors enumerated, the increase in arterial sclerosis and peripheral resistance in the aging of normal human beings seem to be the factors more likely to influence the remarkable slowing of the rate of the second component.

SUMMARY

The measurement and evaluation of an early rate of Na^{24} movement in normal subjects of both sexes is described. The rate of Na^{24} movement, designated as the second component is markedly slowed during the aging process, and the correlation between the rate and age is significant. The rate of the second component is more rapid in women than in men of the same age. The sex difference observed for the average half-time of the second component at the chosen age of 50 years is statistically very significant. The differences observed in the

1161229

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE
Harden B. Jones Committee Papers
BANCROFT/UARC ID NO.
73/112c
COPY
CARTON NO.
3
FOLDER NAME
Early Mixing of Na 24 in Normal Man
NOTES
p 7/7
FOUND BY/DATE FOUND
Susan Stoch 11/15/94

regression coefficients of both sexes are, however, of less statistical significance.

A single measurement and evaluation of the half-time of the second component has a limited value for determining the relationship between the rate of blood mixing of an individual to his chronological age because of the large standard error. More than one measurement and evaluation as well as technical improvements are necessary to decrease this error. The present technique is adequate to study, in a group of subjects, the deviations from the normal regression line of the movement rate versus age.

The authors wish to acknowledge their appreciation to Mrs. Cathrine Cohn for her aid in securing persons for these studies.

REFERENCES

1. Berg, W. E. *Am. J. Physiol.* 140: 507, 1947.
2. Jones, H. B. In: *Medical Physics*, edited by O. Glasser. Chicago: Yr. Bk. Pub., 1950, vol. II.
3. Pace, N., E. Strajman and E. L. Walker. *Federation Proc.* 7: 80, 1948.
4. Strajman, E., G. F. Warner, N. Pace and M. E. Johnston. Unpublished observations.
5. Pace, N., E. Strajman and E. L. Walker. *Science* 111: 652, 1950.
6. DeMoor, J. C. *J. Appl. Physiol.* 6: 460, 1954.
7. Gibson, J. G. and W. A. Evans. *J. Clin. Investigation* 16: 317, 1937.
8. Strajman, E. In preparation.
9. Strajman, E., N. I. Berlin, D. J. Elmlinger and J. Robinson. Unpublished observations.
10. Holman, R. *Am. J. Physiol.* 118: 254, 1937.
11. Drinker, C. K. and M. E. Field. *Am. J. Physiol.* 97: 32, 1931.
12. Pappenheimer, J. R., E. M. Renkin and L. M. Borrero. *Am. J. Physiol.* 167: 13, 1951.
13. Lewis, W. H. *Am. J. Physiol.* 122: 517, 1938.
14. Shock, N. W. *Geriatrics* 1: 232, 1946.

Copied from original in the [illegible] referenced in [illegible] other [illegible] Dept., Physiology, [illegible] to [illegible] Medical Physics, [illegible] versity of California, [illegible]

1161230