THE DETERMINATION OF THE CIRCULATION RATE IN MAN FROM THE ARTERIAL AND VENOUS CO_2-TENSION AND THE CO_2-OUTPUT.

By G. LILJESTRAND AND J. LINDHARD.

(*From the Laboratory for the Physiology of Gymnastics, University of Copenhagen.*)

IN 1870 A. Fick(1) pointed out that the quantity of blood which is driven out from one ventricle of the heart during a given time can be calculated, if the respiratory exchange and the volumes of CO_2 and O_2 in the arterial and venous blood respectively are known. The principle thus introduced has been extensively used in animals by Gréhant and Quinquaud(2) and Zuntz and Hagemann(3) and quite recently with improved technique by Barcroft, Boycott, Dunn, and Peters(4). In man Loewy and v. Schrötter(5), Plesch(6), and Fridericia(7) adopted the same principle as regards the O_2-consumption and O_2-contents of the arterial and venous blood. The determinations of the gases of the arterial and venous blood in man are made indirectly: the arterial and venous tensions of the gases are ascertained, and then the gas volumes contained in the blood at these tensions are determined separately. Important drawbacks of the method are that it is necessary to determine not only the O_2- but also the CO_2-tensions and also in every single case the O-absorption of the blood at these pressures, as this function varies individually and is highly affected by the CO_2-tension. For these reasons it seems very desirable that the performance of the circulation rate determinations after Fick's principle should be improved. From this point of view the investigations of Boothby and Sandiford(8) and of Sonne(9) are of interest.

Boothby and Sandiford (cp. Boothby(10)) did not calculate the volume of blood passing through the lungs from the CO_2-output and the arterial and venous CO_2-tension—though they point out the possibility of such a calculation—but they proceed in the reverse order. From the minute-volume, as determined by the nitrous oxide method of Krogh and Lindhard(11), the CO_2-output and the alveolar CO_2-tension they calculate the venous CO_2-tension. For this calculation they make the assumption that the CO_2-absorption curve for their subject of experiments is the same as that found by Christiansen, Douglas and Haldane(12). The values thus calculated for the venous CO_2-tension are compared with direct determinations. As the CO_2-absorption of the blood increases with lowering of the O_2-tension, the real venous CO_2-tension should truly be calculated and estimated at the existing venous O_2-tension. Boothby and Sandiford, however, simplified the computation in such a manner that they only had to deal with the CO_2-tension in the lungs after complete oxygenation of the blood. Though this tension is much higher than the really existing tension, the CO_2-content of the blood however must be the same. And if the CO_2-absorption curve for oxygenated blood is known, it is easy to calculate from it the venous CO_2-tension for the fully oxygenated blood, a quantity that is also very easily determined approximately directly.

The reasoning of Sonne is quite analogous to that of Boothby and Sandiford, though he takes the minute-volume of the heart as the unknown factor. He also assumes the curve found by Christiansen, Douglas and Haldane to be generally applicable, not only to healthy subjects but also to patients suffering from various diseases, on the assumption that there is no abnormal p_H of the blood. From the curve mentioned he finds that a pressure-difference of 1 mm. Hg corresponds to an alteration in the CO_2-content of 0·4 c.c. for 100 c.c. of blood within physiological pressures. As Boothby and Sandiford he deals only with the CO_2-tension of completely oxygenated blood.

If the assumption of Boothby and Sandiford and of Sonne that the curve of Christiansen, Douglas and Haldane is without correction applicable to other subjects were true, it would be a simple matter to determine the blood-flow through the lungs of man, especially if the venous CO_2-pressure is measured, as they propose, simply after full oxygenation in the lungs. Since, however, the validity of the assumption appears doubtful, it seemed desirable to investigate the method in some detail and also to compare it further with the method hitherto most used, viz. that of Krogh and Lindhard.

Our experiments, which were performed on ourselves, took place several hours after a very light breakfast. After the subject had been sitting quietly for at least half-an-hour, the venous CO_2-pressure was determined according to the technique described by Fridericia. After expiration to residual air the subject took a deep inspiration from a spirometer, containing a mixture of CO_2 and common air, or, in some experiments, air + oxygen. Then the breath was held for two to three seconds, then about half of the inspired air was expired to the spirometer, and the breath held again. After 7–10 seconds, the rest of the inspired air was expired. Of the two expirations, samples were taken from the rubber tube connecting the subject with the spirometer. As time and expirations had been graphically recorded and the residual air of the subjects being known, it was possible to calculate the CO_2 eliminated or absorbed between the two expirations. For details compare Fridericia(7). In order to be sure that the saturation of the hemoglobin should be complete, we introduced in some experiments oxygen in the spirometer.

The respiratory exchange and the number of respirations were determined in respiration experiments, taking place after at least 45 minutes' complete rest. The dead space of both subjects having been determined by the method of Krogh and Lindhard(13),we calculated the alveolar CO_2-pressure from the respiration experiments. The CO_2-absorption curve of the blood was determined by the method published recently by Krogh and Liljestrand(14). On G.L. in all 20 determinations at varying CO_2-pressures and complete oxygenation of the blood were carried out, which have already been published in detail. Here we reproduce only the curve for G.L. On J.L. six determinations were made.

Turning now to the results of our experiments, we give in Table I and Figs. 1 and 2 the values for the venous CO_2-tension in G.L. and J.L.

The values of G.L. (Fig. 1) show a remarkable agreement between the two groups with air and with air + oxygen, which proves that the oxygenation is already complete in the experiments with common air. Experiments with the same CO_2-absorption or elimination per second show however differences in tension amounting to about 2–3 mm. Such differences, the cause of which must be sought for in real changes in the blood, are found not only between experiments from different days but also in experiments performed within half-an-hour (22.11). Fridericia assumes that the values found can be considered to give the real venous CO_2-tension, if the quantity of CO_2 eliminated or absorbed per second does not exceed 1 c.c. Fig. 1 does not support this view with regard to G.L. In those cases where CO_2 is taken up by the body from the air in the lungs (−) there is a marked tendency for the values found to sink with lowering of the quantity of CO_2 that is taken up. And the values on the

TABLE I. Determinations of the venous CO_2-tension.

Time	Bar. mm.	Duration of exp. min.	Air in the lungs l.	CO_2 after the first expiration p. c.	CO_2 after the second exp. p. c.	CO_2 mm.	CO_2 eliminated (+) or absorbed (−) c.c. per sec.	Freq. of the pulse	Subject	Remarks
19. 11.										
1.30	752	0·135	1·83	6·30	6·54	46·1	+0·49	72	G.L.	Air*
1.45	752	0·133	4·06	7·06	6·97	49·1	−0·41	68	,,	,,
2.00	752	0·117	3·52	7·17	6·92	48·8	−1·13	68	,,	,,
22. 11.										
11.00	747·5	0·136	3·33	6·43	6·49	45·4	+0·22	58	,,	Air + oxygen†
11.40	747·5	0·139	3·65	6·19	6·25	43·8	+0·24	55	,,	,, ,,
11.50	747·5	0·141	3·00	5·94	6·19	43·4	+0·81	55	,,	,, ,,
25. 11.										
10.35	748	0·150	3·57	7·46	7·22	50·6	−0·87	65	,,	,, ,,
10.50	748	0·142	2·84	7·53	7·28	51·0	−0·76	63	,,	,, ,,
11.25	748	0·156	2·66	6·84	6·78	47·5	−0·15	62	,,	,, ,,
26. 11.										
10.15	744	0·152	2·97	6·44	6·47	45·1	+0·09	66	,,	Air
10.30	744	0·142	2·79	7·26	6·98	48·7	−0·82	57	,,	Air + oxygen
10.35	744	0·154	2·62	6·32	6·44	44·9	+0·30	66	,,	Air
27. 11.										
10.50	748	0·126	2·82	7·25	7·08	49·6	−0·57	56	,,	,,
11.20	748	0·146	2·40	7·28	7·06	49·5	−0·54	51	,,	Air + oxygen
4. 12.										
11.45	750	0·139	2·38	6·60	6·58	46·2	−0·05	64	,,	Air
15. 11.										
	751	0·216	4·21	6·41	6·61	46·5	+0·59	66	J.L.	Air + oxygen
	751	0·223	4·48	6·62	6·77	47·7	+0·45	—	,,	Air
21. 11.										
11.35	741·5	0·148	3·90	6·32	6·58	45·7	+1·02	64	,,	,,
11.45	741.5	0·153	4·21	7·29	7·24	50·3	−0·21	62	,,	,, ‡
11.55	741·5	0·129	4·23	6·55	7·12	49·4	+2·8	60	,,	Air + oxygen
24. 11.										
11.00	740	0·194	4·20	6·60	6·62	45·8	+0·07	66	,,	Air
11.50	740	0·155	4·41	6·46	6·88	47·7	+1·8	58	,,	Air + oxygen
25. 11.										
11.40	748	0·142	3·74	7·28	7·21	50·5	−0·28	61	,,	,, ,,
11.45	748	0·155	3·61	6·92	6·66	46·6	−0·91	58	,,	Air
26. 11.										
10.45	744	0·142	4·08	7·03	6·91	48·2	−0·52	66	,,	Air + oxygen
11.05	744	0·115	3·86	7·92	7·86	54·7	−0·30	66	,,	Air
11.35	744	0·145	3·78	7·61	7·76	54·1	+0·58	63	,,	Air + oxygen
27. 11.										
11.32	748	0·148	3·71	7·56	7·26	50·8	−1·13	64	,,	,, ,,
11.43	748	0·139	3·56	7·12	7·00	49·0	−0·46	63	,,	Air
28. 11.										
10.20	752	0·151	3·27	6·89	6·86	48·4	−0·99	64	,,	,,
10.52	752	—	—	6·96	6·78	47·8	− ?§	62	,,	Air + oxygen

* 15·28 p.c. oxygen in second sample. † 20·91 p.c. oxygen in second sample.

‡ 15·80 p.c. oxygen in second sample.

§ No graphical registration; from the extreme values for duration of experiment and air in the lungs 21. 11–27. 11 the limiting values −0·46 and −0·96 are calculated.

other side of the equilibrium obviously increase when the CO_2 eliminated is diminished. Thus both sets of values approach a limit very near 46 mm. All values below the equilibrium give the mean 44·8 mm., and those above

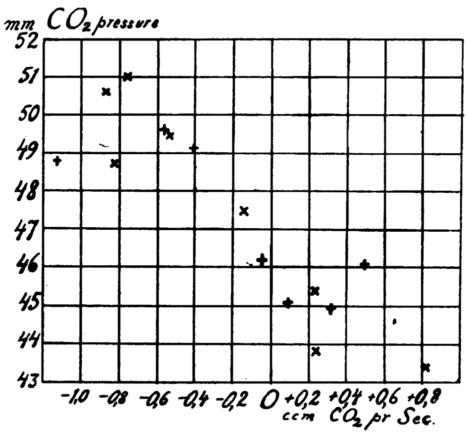

FIG. 1. Venous CO_2-tension of G.L. The abscissa indicates the pressure found in mm. of Hg, the ordinate the amount of CO_2 in c.c. per second that is taken up (−) or given off (+) by the body to the air in the lungs between the two samples (cp. the test). + = experiments with air, × = experiments with air + oxygen.

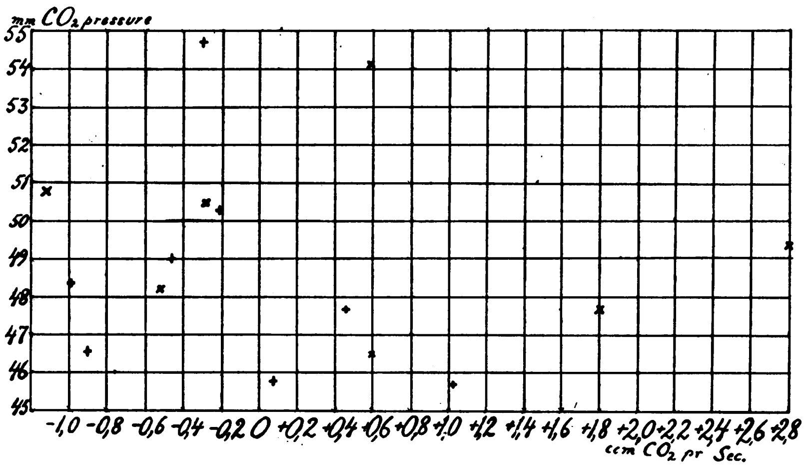

FIG. 2. Venous CO_2-tension of J.L. Indications as in Fig. 1.

it give 49·0 mm. To find the probable average tension, the safest course appears to be to consider only those where the tension equalisation is nearly complete, *e.g.* where not more than 0·5 c.c. CO_2 per second is taken up or given off. The means are for the 3, respectively 5, values above and below the equilibrium 47·6 and 45·4, with 46·4 as the general average. The fact that also those values, where CO_2 is absorbed by the body in smaller quantity than 0·5 c.c. per second, seem to diminish with lowering of the value of the absorption more than the corresponding increase on the other side of the equilibrium, indicates that the most probable value for the mean tension in this subject is very near 46 mm., though at the same time it must be admitted that there is some unavoidable uncertainty.

For J.L. (Fig. 2) the values show a similar though not so pronounced tendency as in G.L. Two determinations, both from the same day and lying the one above, and the other below, the equilibrium, have from unknown reasons given remarkably high values. There seems to be no doubt, however, that the real value on this occasion was high. The values above and below the equilibrium give the means 49·6 and 48·1 mm. respectively, thus giving the average 48·9 mm. If, however, the two extremely high values mentioned are excluded, and this seems to be justified by their great deviation, we get the values 47·1, 49·0 and 48·0 mm. respectively. The uncertainty is undoubtedly greater here than in the series on G.L.

TABLE II. Respiration experiments.

Time	Bar. mm.	Duration of exp. min.	Frequency of resp.	Frequency of pulse	Ventilation per min. l. (0°·760)	CO_2-output c.c.	O_2-consumption	Resp. Quot.	Alveolar CO_2-press. mm.	Subject
25. 11. 11.05	748	3·1	12·6	70	5·68	200	227	0·88	36·0	G.L.
27. 11. 11.00	748	3·0	9·9	60	4·45	167	200	0·83	39·2	„
28. 11. 11.25	752	4·0	13·9	61	6·17	204	233	0·88	34·2	„
2. 12 10.50	755	4·0	11·4	58	5·10	172	208	0·83	35·2	„
4. 12. 12.00	750	4·1	13·7	68	6·05	186	223	0·84	32·1	„
5. 12. 10.55	753	4·3	10·7	56	5·73	215	235	0·915	36·2	„
6. 12. 10.55	734·5	4·1	11·1	67	5·34	199	233	0·86	36·1	„
11.20	734·5	4·1	11·5	61	4·76	170	207	0·82	36·9	„
24. 11. 11.15	740	3·2	6·0	66	4·27	170	219	0·78	35·0	J.L.
26. 11. 11.15	744	6·2	5·4	60	4·18	163	207	0·79	34·0	„
28. 11. 10.28	752	4·1	5·4	62	4·28	175	213	0·82	35·8	„

The experiments for determination of the respiratory exchange and the alveolar CO_2-tension are found in Table II. The total dead space (personal dead space + dead space of valve and mouthpiece of mask) was for G.L. 170 c.c. (37°) and for J.L. 182 c.c. (37°).

From the table the following averages are found. For G.L. the alveolar CO_2-pressure is 35·7 ± 0·75 mm., the CO_2-output 189 ± 6·3 c.c. and the O_2-consumption 221 ± 4·9 c.c. For J.L. the corresponding values are 34·9 mm., 169 and 213 c.c.

The CO_2-absorption of the blood of G.L. is represented by the upper curve Fig. 3. With the blood of J.L. the following six determinations were made (Table III).

TABLE III. CO_2-absorption of the blood from J.L. during rest (37°).

Time	CO_2-pressure in saturator; mm. of Hg	Volumes of CO_2 in 100 volumes of blood
29. 11	23·6	33·6
"	"	33·7
"	51·0	47·3
"	"	48·2
5. 12	41·7	44·4
"	"	44·9

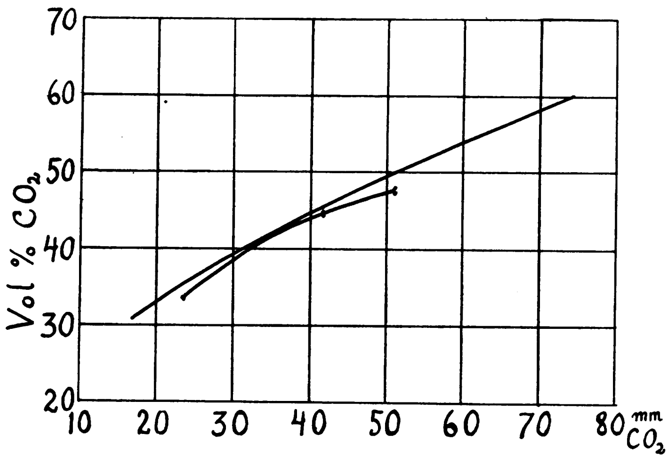

FIG. 3. Upper curve—absorption of CO_2 by blood of G.L. in presence of oxygen and CO_2 (37°). Lower curve—absorption of CO_2 by blood of J.L. in presence of oxygen and CO_2 (37°).

The determinations on J.L. are also plotted in Fig. 3 and give the lower curve. These curves are in this connection of a special interest. They show clearly that the assumption made by Boothby and Sandiford and by Sonne that the curve found by Christiansen, Douglas and Haldane could be applied to all healthy persons is not correct. There is a very distinct difference in the general shape of the curves. In those parts which have the greatest physiological interest, viz. between 30 and 50 mm. pressure, we find for G.L. an increase in the absorption of 5·7 vol. p.c. between 30 and 40 and 4·8 vol. p.c. between 40 and 50 mm. For J.L. the corresponding values are 5·6 and 3·3 vol. p.c. From the curve for J.S.H. (12) we find the values to be about 5·3 and 4·2 respectively.

Thus, when Sonne assumes that the curve is approximately a straight line (for the CO_2-pressures within the living organism) and that a tension-difference of 1 mm. of Hg corresponds to 0·4 c.c. of CO_2 in 100 c.c. of blood, none of these assumptions can be maintained. Also the determinations published by Hasselbalch (15) give evidence that the CO_2-absorption curves of different individuals differ not only as regards the level of the curve but also (at about the same level) as regards the shape of the curves. It seems necessary therefore to determine the curve separately for each subject, if the minute-volume of the heart is to be calculated from it. And this becomes the more necessary, because, as pointed out later, the sources of error in the method are rather great.

From the values obtained we calculate in the following table the blood-flow of our subjects.

TABLE IV. The blood-flow calculated after Fick's principle.

	Mean CO_2-pressure mm. of Hg.		Mean CO_2-contents (vol. p.c.) in						
Subject	venous blood	art. blood	art. blood	venous blood	Difference	CO_2-output c.c. per min.	O_2-consumption c.c. per min.	Minute-volume of blood l. per min.	O_2-consumption per l. blood c.c.
G.L.	46·0	35·7±0·75	47·3	42·1	5·2	189±6·3	221±4·9	3·6	60·6
J.L.	48·0	34·9	46·8	41·6	5·2	169	213	3·3	65·5

Concerning the sources of error in the method, the alveolar CO_2-pressure in the subject G.L., where a relatively large number of experiments was performed, had a mean error of ± 0·75 mm. The mean error of the venous pressure cannot be calculated in this way with regard to the uncertainty of complete equalization in some experiments. Yet it seems fair to assume that the probable error must be at least of the same magnitude as for the alveolar tension. Boothby gives as large an average deviation as 1·8 mm. from 68 determinations during rest; there seems to be no guarantee, however, for complete equalization. Assuming a mean error of 1 mm. for both arterial and venous pressure and a pressure difference of 10 mm., this would involve a mean error for the difference of 1·4 mm., *i.e.* 14 p.c. As for the absorption-curve of the CO_2 of the blood, slight errors in the determination of the shape must have a very great influence, since the absolute difference for the pressure difference in question is small. Obviously errors of at least 10–20 p.c. from this cause must be taken into account. The errors lastly from the determinations of the CO_2-output—though generally not large —augment the uncertainty of the determination of the blood-flow. From these considerations it seems necessary to assume that the method for determination of the blood-flow has an uncertainty of at least some 20 p.c. and during unfavourable conditions much more. The uncertainty of the Krogh-Lindhard method, considered by them to be approximately about 10 p.c., is without doubt much lower than that of the method mentioned.

It seemed to us of interest to compare the results obtained by the method here described with those found by the nitrous oxide method. As, however, the time at our disposal was not sufficient to obtain a reliable series of such determinations, and, as recent experiments made during somewhat different conditions agreed fairly well with previous experiments made under similar conditions, we have found it permissible to use earlier experiments performed after a sufficiently long resting period for comparison. The homogeneity of a series of circulation experiments is not governed by the time interval between each experiment but by the uniformity of the prevailing subjective and objective experimental conditions.

In the case of J.L. we have the following series (7):

	Min. vol. red., l.	O_2-abs. c.c.	O_2 per l. blood c.c.	O_2-abs. per min. c.c.	Min. vol. red., l.	Pulse rate	Output per beat
K. and L. method	13·3	876	63·5	250	3·9	66	60
	8·5	520	61	,,	7·2	63	66
	10·9	710	65	,,	3·8	71	54
	7·8	543	69·5	,,	3·6	70	51
Average			65	250	3·9		
Present method			65·5	213	3·3		
Method of Fridericia			60	250	4·2		

In the case of G.L. the available material is more limited. During favourable conditions we have found by the

K. and L. method (16)	52·5	228	4·3
Present method	60·5	221	3·6

Now it must be borne in mind that the minute volume of the heart is not an independent variable but a function of metabolism. The essential feature in circulation is the oxygen absorption (resp. giving off) per unity volume of blood, and only this function, therefore, can be applied for comparison when metabolism varies. Remembering this the above figures show that in the case of G.L. the present method gives values about 15 p.c. higher than those obtained by the Krogh and Lindhard method. The deviation from mean of the two averages is thus some 7 p.c. or within the limits of error of both methods. For the subject J.L. the values obtained by the two named methods are identical, while a third method, the method of Fridericia, gives 3 p.c. lower values for the oxygen absorption per litre of blood. Also this difference lies of course within the limits of error of the methods concerned. As the large experimental material now at hand does not furnish any base for the assumption that the methods used are vitiated by systematical errors, it must be claimed that we are able to get a fairly reliable expression for the blood-flow through the lungs, when we consider the average of a series of experiments. The methods are all complicated and rather laborious, and owing to the instability of the function concerned and the impossibility to determine the real experimental conditions a single determination may be erroneous.

The method described in the present paper was worked out in the hope of obtaining a method more easy to manage and, if possible, more reliable than that of Krogh and Lindhard. In both directions, however, we were disappointed. The present method requires more apparatus and is appreciably less reliable than the nitrous oxide method.

Summary.

The method of calculating the blood-flow in man on Fick's principle from the arterial and venous CO_2-pressure of the oxygenated blood and the CO_2-output is discussed. Individual variations of the shape of the CO_2-absorption curve of the oxygenated blood make it necessary to determine it separately for each subject.

Determinations during rest performed with the method gave results which showed a satisfactory agreement with determinations according to Krogh-Lindhard's method, considering the rather great uncertainties of the method on Fick's principle.

REFERENCES.

(1) Fick. Verh. d. physik.-med. Ges. in Würzburg **2**, 1872, Sitz.-ber. 1870, p. xvi.
(2) Gréhant and Quinquaud. Compt. rend. Soc. Biol. Ser. **8**, T. 3, p. 159. 1886.
(3) Zuntz and Hagemann. Landwirtsch. Jahrb. **27**, Suppl. 3. 1898.

(4) Barcroft, Boycott, Dunn and Peters. Quart. Journ. of Medic. **13**, No. 49. 1919.
(5) Loewy and v. Schrötter. Ztschr. f. exp. Path. u. Ther. **1**, p. 197. 1905.
(6) Plesch. Ztschr. f. exp. Path. u. Ther. **6**, p. 380. 1909.
(7) Fridericia. Bioch. Ztschr. **85**, p. 307. 1918.
(8) Boothby and Sandiford. Amer. Journ. Physiol. **40**, p. 547. 1916.
(9) Sonne. Deutsch. Arch. f. klin. Med. **124**, p. 358. 1917–18.
(10) Boothby. Amer. Journ. Physiol. **37**, p. 383. 1915.
(11) Krogh and Lindhard. Skand. Arch. f. Physiol. **27**, p. 11. 1912.
(12) Christiansen, Douglas and Haldane. Journ. of Physiol. **48**, p. 244. 1914.
(13) Krogh and Lindhard. Journ. of Physiol. **47**, p. 431. 1913.
(14) Krogh and Liljestrand. Bioch. Ztschr. In the Press. 1920.
(15) Hasselbalch. Bioch. Ztschr. **78**, p. 112. 1916.
(16) Liljestrand. Skand. Arch. f. Physiol. **37**, p. 180. 1918.