THE CEREBRAL BLOOD FLOW IN MITRAL STENOSIS AND ITS RESPONSE TO CARBON DIOXIDE

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Received March 11, 1958

Ever since Kety and Schmidt (1948) showed that the cerebral blood flow (C.B.F.) of normal subjects would increase when carbon dioxide was inhaled, such inhalation has had obvious possibilities in the treatment of cerebral embolism. As it has not been known whether this increase would still occur when mitral stenosis, the commonest cause of cerebral embolism, was present, it was decided to measure the C.B.F. at rest and again during inhalation of 5 per cent carbon dioxide in 12 patients with this disease (Series 1). Since these patients were also being studied as to their suitability for surgical treatment the opportunity was taken to compare the C.B.F. with the clinical status of the patients and with the hæmodynamic findings obtained by cardiac catheterization both at rest and during exercise. This report includes in addition estimations of the C.B.F. at rest of 13 other subjects who suffered from mitral stenosis and were having cardiac catheterization done (Series 2) and of 6 student volunteers who acted as controls (Series 3). The combined series show how the resting C.B.F. of patients with mitral stenosis differs from the normal.

Subjects, Methods, and Procedure

Details of the 12 subjects of Series 1 are given in Table I. None were in congestive heart failure or suffering from active rheumatism. The 13 subjects whose C.B.F. are given who did not inhale CO_2 include six from a series previously reported (Dewar *et al.*, 1953). Six of the other seven patients were from a series not previously published and had been given a dosage of nitroglycerine which proved to be without influence on the C.B.F.; these latter six may be regarded as controls for the reproducibility of the method. None of the subjects in Series 2 or Series 3 were given morphine at any stage of their C.B.F. estimations.

Cerebral Blood Flow was estimated by the nitrous oxide method of Kety and Schmidt (1948), and their standard gas mixtures were used. For Series 2 Scheinberg and Stead's (1949) modification of this technique was used but with corrections for the dead space of the catheter and connecting tubing so as to render the result comparable (Stroud *et al.*, 1954). In all three series the cerebral venous blood samples were collected through a cardiac catheter whose end had been placed in the superior jugular bulb according to the technique described by Dewar *et al.* (1953). Nitrous oxide content of blood was estimated in a Van Slyke manometric apparatus for Series 2 and 3, but for Series 1 where the number of estimations was larger the method of Lawther and Bates (1953), using an infra-red analyser, was substituted; its accuracy was first checked against the Van Slyke apparatus. All samples were analysed in duplicate.

Oxygen Consumption was measured by collection of expired air into Douglas bags. Duplicate air samples were analysed in a Haldane gas apparatus and the oxygen uptake calculated by standard methods.

Oxygen Content of Blood. The hæmoglobin percentage saturation was measured by the method of Molyneux and Pask (1955), slightly modified. The oxygen content and capacity were deduced from the percentage saturation and the hæmoglobin concentration, measured photometrically.

Pressure Recording. Intra-cardiac pressures were recorded on an Elmquist strain gauge manometer, zero being fixed at the subject's sternal angle. Brachial artery pressures were taken with a mercury sphygmomanometer, mean pressures being taken as the diastolic plus a third of the pulse pressure.

Proceedure. No preliminary sedatives were given but quinidine, 0·2 to 0·3 g., was given to those having cardiac catheterization in order to prevent arrhythmias. To the subjects of Series 1 whose investigation took an exceptionally long time a light breakfast of tea and toast was permitted. In the subjects of Series 2 cardiac catheterization was followed after a rest period of at least 45 minutes by an estimation of C.B.F. (13 patients) and after a further half hour's rest by a duplicate estimation (6 patients).

In the subjects of Series 1 to whom exercise was to be given the catheter was continually flushed with a small quantity of 0·1 per cent procaine solution as an additional precaution against

TABLE 1

CARDIOVASCULAR HÆMODYNAMICS OF SERIES 1

Subject	Cardiac rhythm	Digitalis	Functional grading		Pressures (mm. Hg)		Oxygen saturation %		Cardiac index (l/min/ M²)	Calculated mitral valve area (cm.²)	Operation findings
					Pulmonary artery (mean)	Pulmonary capillary (mean)	Brachial artery	Pulmonary artery			
1. E. B. (M)	S.R.	No	I	Rest	20	11	92	61	2·8	1·6	
				Ex.	30	—	93	57	7·8		
2. M. W. (F)	S.R.	No	IV	Rest	17	12	96	73	3·4	1·9	
				Ex.	38	—	97	62	4·1		
3. M. H. (F)	A.F.	Yes	III(a)	Rest	39	27	98	73	2·7	0·9	M.S. +++
				Ex.	48	—	92	55	3·9		
4. N. R. (M)	S.R.	No	IV	Rest	25	21	93	69	3·6	1·4	
				Ex.	30	—	84	c. 33	?3·0		
5. L. F. (F)	S.R.	No	III(a)	Rest	10	Not obt.	97	73	3·0	—	
				Ex.	12	—	97	c. 58	?3·0		
6. R. M. (M)	S.R.	No	II	Rest	8	6	96	76	3·6	>2·5	
				Ex.	17	—	95	48	3·5		
7. J. Mor. (M)	S.R.	Yes	III(b)	Rest	28	18	91	59	2·9	2·2	
				Ex.	52	—	88	38	5		
8. G. W. (M)	A.F.	Yes	II	Rest	20	14	92	67	2·8	1·6	M.S. ++
				Ex.	30	—	91	c. 32	?3·6		
9. A. W. (M)	S.R.	Yes	III(a)	Rest	42	22	88	64	2·5	0·9	M.S. +++
				Ex.	72	—	88	c. 38	?2·7		
10. J. F. (M)	S.R.	No	III(b)	Rest	32	20	93	68	2·5	1·0	M.S. +++ M.I. +
				Ex.	54	—	90	47	6·8		A·S. +
11. J. Mos. (M)	A.F.	Yes	III(b)	Rest	30	Not obt.	86	52	1·9	—	M.S. +++ M.I. +
				Ex.	61	—	76	24	2·3		
12. T. W. (F)	A.F.	Yes	III(a)	Rest	18	15	92	76	4·1	1·7	M.S. ++
				Ex.	28	—	93	53	4·1		

S.R. = Sinus rhythm
A.F. = Auricular fibrillation
M.S. = Mitral stenosis
M.I. = Mitral regurgitation
A.S. = Aortic stenosis

arrhythmias, but this was exchanged for normal saline as soon as the cardiac catheterization was over so that its action would not interfere with the subsequent C.B.F. estimation, though Scheinberg *et al.* (1952) have shown that procaine has an insignificant effect upon C.B.F. When during the catheterization repeated pressure records showed that a steady state of pulse and pressure was present, the resting cardiac output was measured by the direct Fick principle. The patients then exercised in the recumbent position on an ergometer (Bronfin, Dressler, and Ravin, 1950) to the level which previous trials had shown to be the most they could sustain steadily for five minutes. During the last three minutes of this exercise multiple blood samples were taken from the pulmonary and brachial arteries whilst the expired air was collected in a Douglas bag so that the cardiac output could again be estimated. Morphine, 0·01 g., was then given intravenously to allay restlessness and after a rest period of at least 45 minutes the C.B.F. was estimated. Thirty minutes later a second estimation of C.B.F. was made during the inhalation of 5 per cent carbon dioxide using the same gas mixture (CO_2 5 per cent, N_2O 15 per cent, N_2 59 per cent, O_2 21 per cent) as was used by Kety (1948) in his studies on the effect of carbon dioxide on cerebral blood flow in normal subjects, but without his preliminary saturating inhalation of carbon dioxide in air. By an unfortunate oversight systemic blood pressure readings during these C.B.F. studies were taken on only 6 of the subjects in this series.

TABLE II

CEREBRAL HÆMODYNAMICS IN MITRAL STENOSIS AND RESPONSE TO INHALATION OF CARBON DIOXIDE (Series 1)

Subject	Sex and age	Resting					Inhaling 5% CO_2					Percentage increase of C.B.F.	Actual increase of C.B.F.
		C.B.F.	A-V O_2	C.M.R.O_2	M.A.B.P.	C.V.R.	C.B.F.	A-V O_2	C.M.R.O_2	M.A.B.P.	C.V.R.		
1. E. B.	M 17	48	—	—	—	—	63	—	—	—	—	+31	+15
2. M. W.	F 32	43	5·8	2·5	76	1·8	52	5·2	2·7	81	1·6	+21	+9
3. M. H.	F 35	34	8·2	2·8	70	2·0	45	7·0	3·2	83	1·8	+32	+11
4. N. R.	M 35	38	—	—	—	—	52	—	—	—	—	+37	+14
5. L. F.	F 39	42	5·7	2·4	85	2·0	52	4·2	2·2	80	1·5	+24	+10
6. R. M.	M 39	24	11·3	2·7	—	—	49	6·0	3·0	—	—	+104	+25
7. J. Mor.	M 44	34	—	—	—	—	43	—	—	—	—	+26	+9
8. G. W.	M 42	29	10·4	3·0	80	2·8	36	8·0	2·9	95	2·6	+24	+7
9. A. W.	M 45	42	6·2	2·6	73	1·8	40	6·6	2·6	84	2·1	− 5	−2
10. J. F.	M 46	43	5·4	2·3	82	1·9	44	5·8	2·6	96	2·2	+2	+1
11. J. Mos.	M 49	34	8·3	2·8	—	—	45	5·2	2·3	—	—	+32	+11
12. T. W.	F 52	23	—	—	—	—	34	—	—	—	—	+48	+11
Mean Values	40	36	7·7	2·6	78	2·1	46	6·0	2·7	87	2·0	+31	+10

C.B.F. = Mean cerebral blood flow (ml./100 gm. brain/min.).
A-V O_2 = Mean arterial-cerebral venous oxygen difference (ml. O_2/100 ml. blood) over ten-minute period.
C.M.R. O_2 = Mean cerebral oxygen consumption (ml. O_2/100 gm. brain/min.).
M.A.B.P. = Mean arterial blood pressure (mm. mercury) over ten-minute period.
C.V.R. = Mean cerebral vascular resistance (mm. mercury/one ml. blood/100 gm. brain/min.) over ten-minute period.

RESULTS

The results are given in Tables I–IV, and full details of the subjects exercised in Table I.

The C.B.F. was measured twice in 6 patients of Series 2, the differences affording useful evidence of the repeatability of the method. The standard deviation of these repeat measurements is 4·3 ml., and this with 6 degrees of freedom means that at the usual 95 per cent confidence level a single observation will lie within $\pm$ 10 ml. of the true value. From the data given by Kety and Schmidt in their original series (1948) the standard deviation of repeat estimations on the same side in the same case can be shown to be 4·6 ml.

TABLE III

CARDIAC STATUS AND CEREBRAL HÆMODYNAMICS IN MITRAL STENOSIS (Series 2)

Subject	Sex and age	Cardiac rhythm	Digitalis	Functional grading	Pulmonary artery mean pressure (mm. Hg)	Operation findings	C.B.F.		A-V O_2		CMR O_2		M.A.B.P.		C.R.V.	
							1	2	1	2	1	2	1	2	1	2
1. M. S.	F 29	S.R.	No	III(b)	64	M.S. ++	38	—	—	—	—	—	75	—	2·0	—
2. E. C.	F 38	A.F.	Yes	III(a)	29	M.S. ++	42	—	—	—	—	—	77	—	1·8	—
3. N. S.	F 22	S.R.	Yes	II	20+	M.S. ++ M.I. ++	58	—	—	—	—	—	81	—	1·4	—
4. M. G.	F 32	S.R.	No	III(a)	45+	—	48	—	—	—	—	—	91	—	1·9	—
5. E. G.	F 38	A.F.	Yes	IV	65+	M.S. ++	28	—	—	—	—	—	78	—	2·8	—
6. W. R.	M 39	S.R.	No	IV	66	M.S. +++	47	—	—	—	—	—	93	—	2·0	—
7. F. G.	M 49	A.F.	Yes	III(a)	25	M.S. +++ M.I. +	37	—	—	—	—	—	—	—	—	—
8. G. W.	M 38	A.F.	Yes	III(a)	29	M.S. +++	39	35	—	—	—	—	80	84	2·1	2·4
9. O. A.	F 25	S.R.	Yes	III(b)	29	M.S. ++	51	40	8·2	8·2	4·2	3·3	78	85	1·5	2·1
10. F. I.	F 29	S.R.	No	III(a)	—	M.S. +	63	57	8·3	8·7	5·2	5·0	91	95	1·5	1·7
11. H. B.	M 35	A.F.	Yes	III(b)	77	M.I. ++	27	33	8·2	8·1	2·2	2·7	96	95	3·6	2·9
12. J. C.	M 31	A.F.	Yes	III(a)	23	M.S. ++	30	27	6·0	6·8	1·8	1·8	90	92	3·0	3·4
13. F. S.	M 35	S.R.	No	III(a)	25	M.S. +++	29	28	11·3	11·3	3·2	3·1	91	84	3·2	3·0
Mean values	34	—	—	—	—	—	41	37	8·4	8·6	3·3	3·2	85	89	2·2	2·3

C.B.F.=Mean cerebral blood flow (ml./100 gm. brain/min.).
A-V O_2=Mean arterial-cerebral venous oxygen difference (ml. O_2/100 ml. blood) over ten-minute period.
C.M.R. O_2=Mean cerebral oxygen consumption (ml. O_2/100 gm. brain/min.).
M.A.B.P.=Mean arterial blood pressure (mm. mercury) over ten-minute period.
C.V.R.=Mean cerebral vascular resistance (mm. mercury/ one ml. blood/100 gm. brain/min.) over ten-minute period.
S.R.=Sinus rhythm.
A.F.=Auricular fibrillation.
M.A.=Mitral stenosis
M.I.=Mitral incompetence.

TABLE IV

CEREBRAL HÆMODYNAMICS IN NORMAL SUBJECTS
(Series 3)

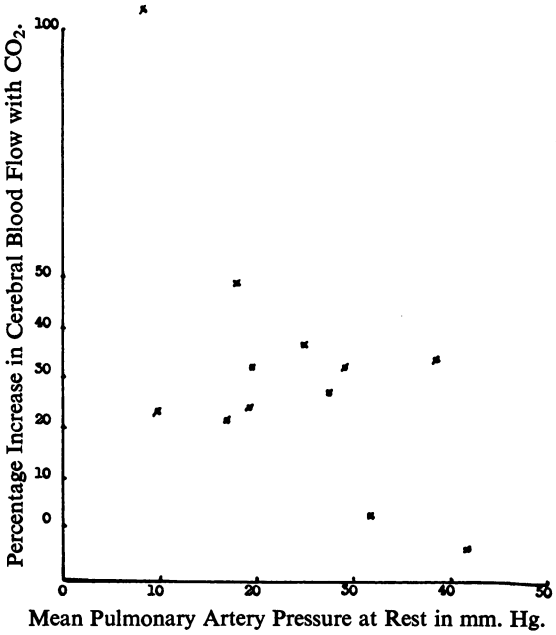
Subject	Sex	Age	C.B.F.	A-V O_2	C.M.R. O_2	M.A.B.P.	C.V.R.
J. Co.	M	21	50	7·8	4·0	83	1·9
J. Ca.	M	22	56	7·1	4·0	96	1·5
J. M.	M	22	44	7·4	3·3	87	2·0
M. R.	M	22	51	5·3	2·7	70	1·4
E.R.	M	23	65	4·9	3·2	102	1·6
J. S.	M	24	72	5·6	4·0	90	1·3
Mean		22	56±10	6·4±1·2	3·5±0·6	88±11	1·6±0·3

C.B.F.=Mean cerebral blood flow (ml./100 gm. brain/min.).
A-V O_2=Mean arterial-cerebral venous oxygen difference (ml. O_2/100 ml. blood) over ten-minute period.
C.M.R. O_2=Mean cerebral oxygen consumption (ml.O_2/100 gm. brain/min.).
M.A.B.P.=Mean arterial blood pressure (mm. mercury) over ten-minute period.
C.V.R.=Mean cerebral vascular resistance (mm. Hg/one ml. blood/100 g. brain/min.) over ten-minute period.

These results show that the resting C.B.F. in cases of mitral stenosis is low. The mean C.B.F. of Series 1 and 2 is 39 ml./min./100 g. of brain, S.D. ± 12, compared with the figure of 56 ml., S.D. ± 10, from the normal subjects of Series 3 and with Kety and Schmidt's normal figure of 54 ± 12. The difference is highly significant, $P < 0.01$. In the patients whose hearts were in sinus rhythm the C.B.F. was higher, 43 ml./min./100 g. than in those whose auricles were fibrillating, 32 ml./min./100 g.

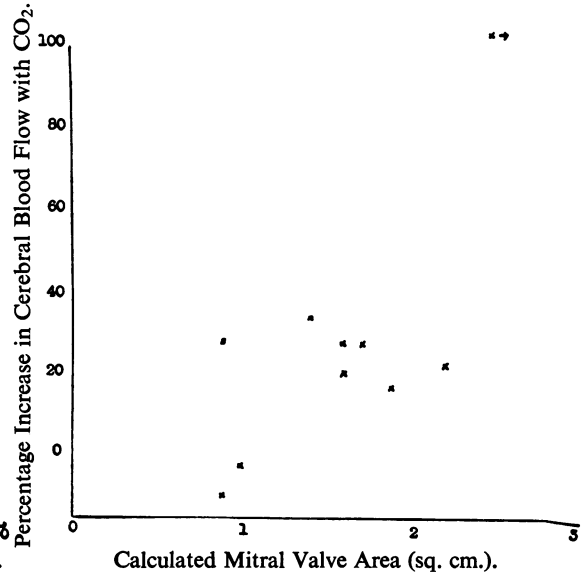
The low C.B.F. of these cases of mitral stenosis is associated with a much increased cerebral vascular resistance, 2·2 mm. Hg/ml. blood/min./100 g. brain tissue (Series 1 and 2) compared with the normal of 1·6 mm. (Series 3, and Kety and Schmidt, 1948), but an only slightly decreased blood pressure—85 mm. Hg. in Series 1 and 2 and 88 mm. Hg in Series 3.

If morphine is not given the oxygen consumption of the brain remains normal at 3·3 ml./min./100 g.



Mean Pulmonary Artery Pressure at Rest in mm. Hg.
$r = -0.62$ $P < 0.05$

FIG. 1.—Graph showing relationship between resting pulmonary artery pressure and increase in C.B.F. induced by inhalation of CO_2.



Calculated Mitral Valve Area (sq. cm.).
$r = +0.71$ $P < 0.02$

FIG. 2.—Relation between percentage increase in cerebral blood flow with CO_2 and calculated mitral valve area.

of brain tissue (Series 2) and this is made possible by an increased oxygen extraction by the tissues such as occurs in other parts of the body in mitral disease (Donald *et al.*, 1954), resulting in an increased arterio-jugular venous oxygen content difference of 8·5 ml. per 100 ml. compared with the normal of 6·4 ml. per 100.ml. If morphine is given as in Series 1 then the oxygen consumption falls, 2·6 ml./min./100 g. of brain tissue, as has been found in normal subjects by others (Moyer *et al.*, 1957), and the arteriovenous oxygen content difference correspondingly decreases, 7·7 ml. per 100 ml.

On inhalation of carbon dioxide the C.B.F. of the 12 cases of Series 1 increased by a mean extent of 31 per cent. The increase occurred in 10 out of the 12 subjects tested, a change that is statistically significant, $P < 0.01$. Of the 6 subjects upon whom information was obtained the mean arterial blood pressure rose in 5 and the cerebral vascular resistance declined in 4.

Attempts to correlate the resting C.B.F. with any of the observed factors in the hæmodynamic studies, namely the functional grading, pulmonary artery pressure at rest and on exercise, pulmonary capillary pressure, arterial-mixed venous oxygen content difference, percentage saturation mixed venous blood, and cardiac index at rest and on exercise were completely unsuccessful.

A similar failure was encountered with the figure for C.B.F. during the inhalation of carbon dioxide. When, however, the resting pulmonary artery pressure was plotted against the percentage increase in C.B.F. induced by CO_2 inhalation a significant, $P<0{\cdot}05$, inverse relationship appeared (Fig. 1). When the mitral valve area of these same cases was calculated by the method of Gorlin and Gorlin (1951) and also plotted against the increase of C.B.F. induced by the inhalation, a rather more significant, $P<0{\cdot}02$, and this time direct, relationship was observed (Fig. 2).

Discussion

Technique. The average age of the 6 student volunteers who acted as normal controls was much less than those of the subjects suffering from mitral stenosis, but it has been shown that cerebral blood flow does not change significantly with age below 45 years (Heyman *et al.*, 1953) and the C.B.F. and other parameters in this normal series agree closely with those of other investigators (Kety and Schmidt, 1948; Shenkin and Novack, 1954).

The subjects of Series 1 whose investigations took an exceptionally long time to complete were not in a truly basal state during the study of their cardiovascular hæmodynamics and this may have affected the results even though only one of them (No. 12) had a resting cardiac index much above the normal.

The cardiac outputs during exercise were estimated as the mean of the last three minutes of a five-minute period since Donald *et al.* (1954) found by minute-to-minute studies of cardiac output during exercise in a similar group of rheumatic patients that 12 out of 16 attained a steady state of arterio-venous oxygen differences and of oxygen uptake within two minutes of the start. In the present series the proportion was very similar, 8 out of 12. A longer period of exercise would have been very poorly tolerated and two of the subjects could only complete 4 minutes; in Case 4 this was due to the development of pulmonary œdema. The derived cardiac outputs of them and of two other subjects who also did not attain a steady state are therefore distinguished by a question mark in Table I and the figures given for the oxygen saturation of their pulmonary artery blood are approximations only.

Results. The low figure for cerebral blood flow and the high arterio-jugular venous oxygen content difference in these cases of mitral stenosis is in keeping with the reduction of regional blood flow to other areas which Donald *et al.* (1954) have found in a similar series of cases. It is produced predominantly by an increase of cerebro-vascular resistance and is associated but not closely correlated with the reduction of cardiac output usually found in such patients (Ferrer *et al.*, 1952). It is of interest that the mean cerebral blood flow of seven cases of mitral stenosis in heart failure collected from previously reported cases (Scheinberg, 1950; Novack, 1953; Moyer *et al.*, 1952) is 40 ml./min./100 g. compared with the figure of 39 ml. reported here for patients not in failure, and this correlates well with the finding of Novack (1953) that in cases of cerebral arteriosclerosis the C.B.F. was not significantly different whether the subjects were in failure or not. Further investigation, in particular determination of *p*H and of pCO_2 values would be needed to show whether the increased cerebral vascular resistance in mitral stenosis is induced by the hyperventilation which is commonly found in this disease (Ferrer *et al.*, 1952); in the present group of cases (Series 1) the mean resting ventilation at 3·8 l./sq. metre/min. at standard pressure and body temperature was normal.

The 31 per cent mean increase of C.B.F. on inhalation of 5 per cent CO_2 was less than the 41 per cent increase observed by Novack *et al.* (1953) and much less than the 75 per cent increase noted by Kety and Schmidt (1948), but since Kety's preliminary saturating mixture of CO_2 in air was not given before the estimation of C.B.F. was begun this must be considered a minimum figure. It did not correlate closely with most of the cardiovascular parameters examined, but the pulmonary artery pressure at rest and the calculated mitral valve area did have a statistically significant relationship to it. In the case of the calculated mitral valve area (which is independent of the basal state of the subject and calculated from figures obtained at rest) the relationship was more significant, $P<0{\cdot}02$,

than in the case of the pulmonary artery pressure, but even so the form of this relationship was largely determined by three extreme figures, the remainder lying rather closely together, so that too much should not be made of it.

These results do suggest that inhalation of 5 per cent carbon dioxide in air could be a useful therapeutic measure in the treatment of cerebral embolism. Whether such treatment could be instituted promptly enough and without deleterious effect on the patient's cardiovascular system or general condition are, however, questions that still remain to be answered.

Summary

The cerebral blood flow was measured by the nitrous oxide technique in two series of 12 and 13 subjects suffering from mitral stenosis and was found to be significantly less than normal owing to an increase in the cerebral vascular resistance. The oxygen consumption of the brain was normal, however, unless morphine had been given when it was found to be depressed.

On inhalation of 5 per cent carbon dioxide in air by the 12 patients of one series, the cerebral blood flow increased by a mean of 31 per cent. The degree of this increase appeared to be related to the calculated mitral valve area and also, inversely, to the resting pulmonary artery pressure but not to the other hæmodynamic factors estimated at rest and on exertion.

It is suggested that inhalation of 5 per cent carbon dioxide merits further study as a means of treating cerebral embolism when it occurs in patients suffering from mitral stenosis.

This work was carried out during the tenure by one of us (L.A.G.D.) of a Luccock Fellowship of King's College in the University of Durham. Our thanks are due to Professor A. A. Harper and the Staff of the Department of Physiology for the construction of the ergometer and for loan of apparatus, to Dr. S. W. Davidson and Dr. C. K. Warrick for radiological facilities, to Dr. N. R. Rowell for technical assistance, to Mr. D. J. Newell for much help and advice on statistics, to the medical students who acted as volunteers for the normal C.B.F. estimations, and to Dr. S. G. Owen and Mr. A. R. Jenkins for permission to use some of their figures.

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