CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION IN NEUROSYPHILIS

By JOHN L. PATTERSON, JR., ALBERT HEYMAN, AND FENWICK T. NICHOLS, JR.

(From the Departments of Physiology and Medicine, Emory University School of Medicine, and the Clinic for Genito-infectious Diseases, Grady Memorial Hospital and the Georgia Department of Public Health, Atlanta, Ga.)

(Submitted for publication February 10, 1950; accepted, July 10, 1950)

The blood vessels of the brain are involved to a major extent in the pathologic changes of late neurosyphilis. Narrowing or obliteration of the vascular lumen frequently results. In dementia paralytica the smaller blood vessels, particularly the capillaries, show the more marked changes, while the medium-size and larger arteries are principally affected in meningovascular syphilis (1). Nerve cell destruction and cortical atrophy occur in both conditions, but are usually more striking and widespread in dementia paralytica.

Functional changes in the cerebral circulation and metabolism would be expected to accompany such anatomical alterations. A diminution in total intracranial blood flow has been found in severely demented patients with general paresis (2), but the method used is now believed to yield abnormally low values. It very probably gives a correct indication, however, of the direction of change in flow. Himwich and Fazekas (3) reported a definite reduction in the cerebral arteriovenous oxygen difference in a patient with dementia paralytica, while Wortis, Bowman and Goldfarb (4) found only a slight diminution of questionable significance in a series of 18 patients.

The recent development of Kety and Schmidt (5) of the nitrous oxide method for the determination of cerebral blood flow (CBF) has provided a reasonably accurate technique for the study of the cerebral circulation and metabolism. The present report presents studies with this technique on 58 patients with various types of neurosyphilis and on 16 control subjects.

METHODS

The subjects with neurosyphilis were either patients on the wards of Grady Memorial Hospital or out-patients in the Genito-infectious Disease Clinic. There were 26 patients with dementia paralytica, nine with meningovascular syphilis, and 23 with asymptomatic neurosyphilis.

The majority of patients with paresis had moderately or far advanced dementia, the duration of which varied from two to 18 months, and averaged 10 months. Most of the patients with meningovascular syphilis were studied within a few weeks after the occurrence of an acute vascular syndrome, such as hemiplegia or cranial nerve palsy. The duration of the infection in the patients with asymptomatic neurosyphilis varied from two to 28 years. The only evidences of neurosyphilis on physical examination in this latter group of patients were pupillary abnormalities in two individuals.

All of the patients with neurosyphilis had abnormal spinal fluid findings, consisting of increased cell counts, elevated protein content, and a strongly positive Wassermann reaction. The average ages in the different groups were: dementia paralytica, 46 years; meningovascular syphilis, 44 years; and asymptomatic neurosyphilis, 38 years.

The control group of 16 subjects had an average age of 34 years and consisted of patients who were convalescing from various acute illnesses, such as pneumonia and gonococcal arthritis. There was no evidence of intracranial complication in any of these patients. In the patients with neurosyphilis, the determinations were carried out either before penicillin or fever therapy was begun or within a few days after the beginning of treatment. All subjects were afebrile at the time of study and the determinations were made with the patients in the supine position. If the patient showed undue anxiety or visible hyperventilation during the procedure, the determination was rejected as invalid.

The effects of penicillin and fever therapy were studied in 17 patients with neurosyphilis. Six patients with dementia paralytica and one with meningovascular syphilis were given malarial fever therapy combined with penicillin, while five patients with dementia paralytica and five with meningovascular syphilis received penicillin alone. Fever therapy for each case consisted of an average of 10 malarial paroxysms with approximately 50 hours of temperature above 103° F. The total dosage of penicillin was 4.8 to 6.0 million units given in divided doses every three hours for a period of eight to 12 days. A complete neurologic and mental status examination was done on each patient before and after treatment.

The cerebral blood flow was determined by the method of Kety and Schmidt, with minor modifications. The blood sampling procedure was simplified by connecting the sampling syringes directly to the needle in the in-

ternal jugular vein and to the needle in the femoral artery. The area between the arterial and venous nitrous oxide curves was measured by use of a planimeter rather than by calculation with the trapezoid rule. The difference between the results obtained by the two methods was found to be negligible, and the planimetric method was used because of its simplicity.

The arterial and venous oxygen and carbon dioxide contents were obtained from samples drawn just before and at the end of the flow procedure. If the arteriovenous difference of these gases had changed during the procedure by more than 2 volumes per cent, the test was rejected as invalid. The cerebral oxygen consumption ($CMRO_2$) was obtained from the product of the blood flow and the arteriovenous oxygen difference.

The analyses of blood for nitrous oxide were done by the method of Orcutt and Waters (6), as modified by Kety and Schmidt, and for carbon dioxide and oxygen by the Van Slyke-Neill manometric techniques (7), also as modified by Kety and Schmidt for blood containing nitrous oxide. Recent studies in this laboratory suggest that the use of Baker saponin together with the modifications, published in 1943, of the original method of Van Slyke and Neill for oxygen analysis may account for the slightly low value for cerebral arteriovenous oxygen difference noted in the control subjects.

The partition coefficient of nitrous oxide between the blood and the brain in paresis was found to be the same as in normal brain (8). The original method of calculating the amount of nitrous oxide taken up by the brain was therefore used without change. In order to rule out the possibility of increased contamination of internal jugular blood by extracerebral venous blood, the period of inhalation of nitrous oxide was increased to 14 minutes in 14 patients with paresis. The differences between the blood flows calculated for 14 minutes and for 10 minutes did not indicate excessive admixture.

Mean arterial pressure was obtained from a damped mercury manometer connected to the femoral arterial needle. The cerebral vascular resistance (CVR) was calculated by dividing the average arterial pressure during the flow procedure by the cerebral blood flow. It represents the mean perfusion pressure required to produce a flow of 1 cc. of blood through 100 Gm. of brain per minute.

RESULTS

The mean values and standard deviations obtained in the control subjects and in the various groups of patients with neurosyphilis are given in Table I.

Cerebral blood flow. The mean value for cerebral blood flow in the control subjects was 58 cc./100 Gm. brain/min. (Figure 1). In the patients with asymptomatic neurosyphilis the distribution of the cerebral blood flow values and the mean were not significantly different from those found in the control subjects ($p > .1$).

In the subjects with meningovascular syphilis the mean CBF was 38 cc./100 Gm. brain/min., or 66 per cent of normal. This reduction was statistically significant ($p < .001$). The reduction of blood flow did not correlate with the clinical state. Some of the patients with the lowest flow values had only mild meningovascular manifestations, such as a transient ophthalmoplegia, whereas patients who had had hemiplegia and coma sometimes showed CBF values approaching normal.

The larger group of patients with dementia paralytica showed a similar reduction in CBF

TABLE I

Mean values and standard deviations in control subjects and in patients with untreated neurosyphilis

	Control subjects (16)		Asymptomatic neurosyphilis (23)		Meningovascular syphilis (9)		Dementia paralytica (26)	
	Mean*	σ	Mean	σ	Mean	σ	Mean	σ
Cerebral blood flow cc./100 Gm./min.	58	± 7	55	±10	38	± 8	42	± 9
Cerebral oxygen consumption cc./100 Gm./min.	3.1	± .4	3.1	± .6	2.4	± .5	2.2	± .7
Cerebral vascular resistance mm. Hg/cc./100 Gm./min.	1.8	± .4	2.0	± .5	2.8	± .5	2.4	± .7
A-V oxygen difference volumes %	5.5	± .9	5.7	± .1	6.5	± 1.5	5.4	± 1.3
Respiratory quotient†	1.06	± .2	1.02	± .18	.95	± .27	1.03	± .24
Mean arterial blood pressure mm. Hg	105	±22	106	±14	104	±13	96	±14
Hematocrit	38	± 4	41	± 5	43	± 5	39	± 4

* All mean values have been calculated from the data on individual patients.

† This function was determined in 13 of the control subjects, 10 patients with asymptomatic neurosyphilis, six with meningovascular syphilis, and 15 with dementia paralytica.

Figures in parenthesis indicate number of patients in each group.

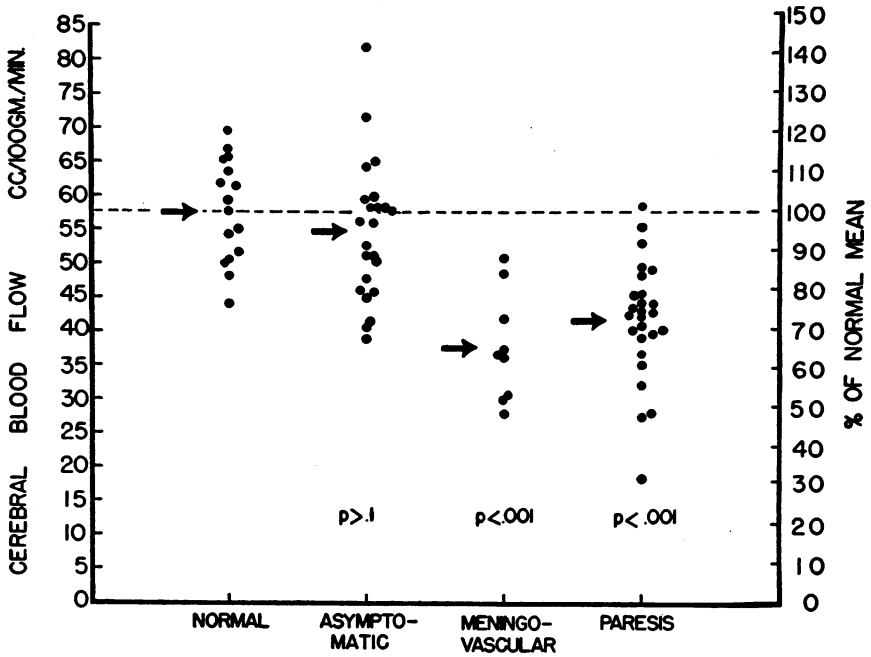

FIG. 1. THE VALUES OBTAINED FOR CEREBRAL BLOOD FLOW IN THE INDIVIDUAL PATIENTS IN THIS STUDY

The arrows point to the mean value in each group. The broken line indicates the mean value in the control subjects.

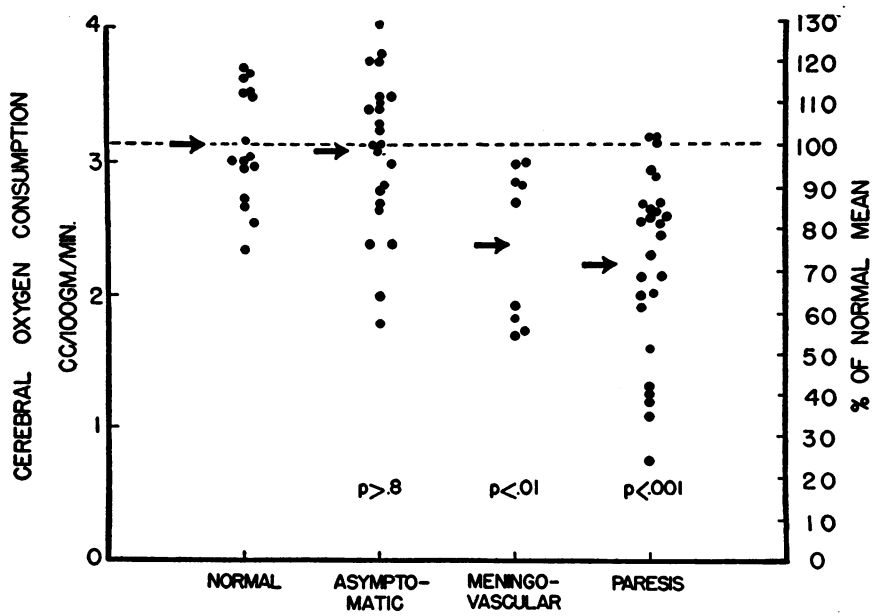

FIG. 2. VALUES FOR CEREBRAL OXYGEN CONSUMPTION IN THE INDIVIDUAL PATIENTS IN THIS STUDY

The arrows indicate the mean value in each group. The broken line indicates the mean value in the control subjects.

with a mean value of 42 cc./100 Gm. brain/min., or 72 per cent of normal. The distribution of these values and the mean reduction in CBF were statistically significant ($p < .001$). The greatest reduction in CBF usually occurred in patients with the most advanced degree of dementia, but in general there was poor correlation between the cerebral blood flow and the degree of mental deterioration.

The hematocrit reading in the various groups of patients was not significantly different and would not be expected to influence the mean CBF values (Table I).

Cerebral oxygen consumption. The mean $CMRO_2$ in the control subjects was 3.1 cc./100 Gm. brain/min. (Table I, Figure 2), a value agreeing with the figure of 3.3 obtained by Kety and Schmidt. The average $CMRO_2$ and the distribution of the results in the patients with asymptomatic neurosyphilis were very similar to those obtained in the control group. The patients with meningovascular syphilis, however, showed a diminished cerebral oxygen uptake with an average of 2.4 cc., or 77 per cent of normal. The distribution of these values is significantly different from that of the controls ($p < .01$).

The patients with dementia paralytica exhibited a similar diminution in oxygen consumption, the mean value being 2.2 cc./100 Gm. brain/min., or 73 per cent of normal. Marked reductions in $CMRO_2$ were noted in several patients with paresis, the values in these instances being less than 40 per cent of normal. In one patient with far advanced dementia, the oxygen consumption was only 0.76 cc./100 Gm. brain/min., or 24 per cent of the normal mean. A definite correlation could usually be made between the degree of mental deterioration and the reduction in the cerebral oxygen consumption in these patients. The $CMRO_2$ in seven patients with moderate degrees of mental deterioration was 2.7 cc., while 12 patients with marked dementia and six with extreme degrees of dementia had values of 2.3 and 1.6 cc., respectively.

The cerebral respiratory quotient (carbon dioxide arteriovenous difference divided by oxygen arteriovenous difference) in the control subjects, as well as the various groups of neurosyphilitic patients, was approximately unity (Table I). Other workers (5, 9) have also obtained similar values in normal individuals.

Cerebral vascular resistance. In the control subjects, the average value for the CVR was 1.8 mm. Hg/cc./100 Gm. brain/min. (Table I). In the patients with asymptomatic neurosyphilis the mean CVR was not significantly different ($p >$

TABLE II

Changes following treatment of six patients with meningovascular syphilis

Patient	Clinical state	Illness duration (days)	Therapy	CBF cc./100 Gm./min.		$CMRO_2$ cc./100 Gm./min.		CVR mm. Hg/cc./100 Gm./min.		Clinical outcome
				Before therapy	After therapy*	Before therapy	After therapy*	Before therapy	After therapy*	
J. H.	Sudden syncope; temporary confusion	5	Penicillin Fever	51	55	2.9	3.5	2.0	1.9	Complete recovery
J. W.	Chronic headache; sudden confusion; transient nerve palsies	15	Penicillin	45	36	2.7	1.6	2.2	3.5	Complete recovery
B. B.	Ophthalmoplegia; fixed pupils	44	Penicillin	42	52	1.7	3.0	2.6	2.1	Complete recovery
A. J.	Progressive abducens palsy; fixed pupils	?	Penicillin	36	43	2.7	3.2	3.7	3.2	No change
R. L.	Hemiplegia; abducens palsy	5	Penicillin	31	47	3.0	2.4	2.9	1.9	Paralysis improved but developed paresis
R. D.	Repeated attacks of hemiplegia	21	Penicillin	28	44	1.7	2.8	3.1	2.1	Developed another vascular accident
Mean				39	46	2.5	2.7	2.8	2.5	
Mean change %					18†		10†		−11†	

* Post-treatment studies performed an average of three months after treatment completed.
† Difference between means before and after treatment not statistically significant.

TABLE III

Changes following treatment of 11 patients with dementia paralytica

Patient	Severity dementia	Duration dementia (months)	Clinical remarks	Therapy	CBF cc./100 Gm./min.			$CMRO_2$ cc./100 Gm./min.			CVR mm. Hg/cc./100 Gm./min.			Clinical outcome
					Before treatment	1st Post-treatment	2nd Post-treatment	Before treatment	1st Post-treatment	2nd Post-treatment	Before treatment	1st Post-treatment	2nd Post-treatment	
S. H.	No psychosis	2	Somatic changes	Penicillin	49	50		3.2	2.4		2.3	2.5		Complete recovery
J. D.	Moderate	6	Juvenile paresis	Penicillin	56	52		3.1	2.9		1.7	1.8		No change
B. P.	Marked	6	Transient hemiplegia	Penicillin, fever	43	42		2.6	2.1		2.3	2.4		No change
J. F.	Marked	10	Progression during therapy	Penicillin, fever	48	36		2.6	2.4		2.7	2.7		Slight improvement
A. O.	Marked	12	Simple dementing type psychosis	Penicillin, fever	40	47	55	2.6	3.6	3.3	2.0	2.0	1.8	Nearly complete recovery
J. E.	Moderate	5	Paroxysmal cold hemoglobinuria	Penicillin	43	54	47	2.5	3.3	2.4	1.6	1.7	2.0	Complete recovery
J. H.	Extreme	9	Simple dementing type psychosis	Penicillin	44	46	42	2.3	2.7	2.8	2.0	2.7	2.2	Significant improvement but residual symptoms
R. T.	Marked	4	Convulsions	Penicillin, fever	44	45		1.9	2.8		2.1	2.2		Complete recovery
G. A.	Extreme	?	Syncopal attacks	Penicillin, fever	40	48	42	1.3	2.7	2.3	2.4	2.0	2.0	Significant improvement but residual symptoms
D. W.	Marked	5	Convulsions	Penicillin, fever	27	39	53	1.2	3.0	3.6	3.0	1.9	1.6	Nearly complete recovery
C. C.	Moderate	?	Paranoia	Penicillin	39	37	38	1.1	1.1	3.0	2.4	3.0	3.0	Nearly complete recovery
Mean in 11 patients					43	45		2.2	2.6		2.2	2.3		
Mean change %‡						5			18			1		
Mean in six patients					39	45	46	1.8	2.7*	3.0†	2.2	2.2	2.1	
Mean change%‡						15	18		49	62			6	

‡ Compared with pre-treatment value.
Significance of difference from pre-treatment value: *p = 0.1; †.05>p>.02.
p values for remainder of means > .2.

.3). However, in meningovascular syphilis and in dementia paralytica, a significant increase in the CVR was found, the mean values being 2.8 ($p < .01$) and 2.4 ($p < .001$), respectively. The levels of the mean arterial pressure showed only small differences in the various groups of subjects.

The effect of treatment in meningovascular syphilis and dementia paralytica. In six patients with meningovascular syphilis, cerebral blood flow determinations were repeated at an average interval of three months following treatment. At this time four of them showed an appreciable increase in CBF, one showed a slight fall, while one patient had no significant change. In two patients the $CMRO_2$ increased considerably; in one, it decreased; there were only slight changes in the remaining three cases (Table II). In general, the correlation between the changes in the CBF and $CMRO_2$ and the clinical course following therapy in this group of patients was not striking.

Studies were also repeated in 11 of the patients with dementia paralytica an average of four months following treatment (Table III). The changes in the cerebral blood flow were not consistent. The cerebral oxygen consumption, however, generally showed a marked increase following therapy in the patients with low pre-treatment values. In patients with relatively high values before treatment, the response of the $CMRO_2$ was variable (Figure 3). These studies were repeated in six of the 11 patients at a mean interval of nine months following treatment, at which time little further change was found in most patients in either CBF or $CMRO_2$. One patient (D. W), however, exhibited a considerable increase in CBF, while another patient (C. C.) showed a marked rise in $CMRO_2$ over the first post-treatment value.

The change in cerebral oxygen consumption in the individual patient could be correlated to some extent with change in mental state. Each of the three patients with dementia paralytica who showed little or no clinical improvement had a small decrease in $CMRO_2$. Of the eight patients with definite improvement, six had a considerable

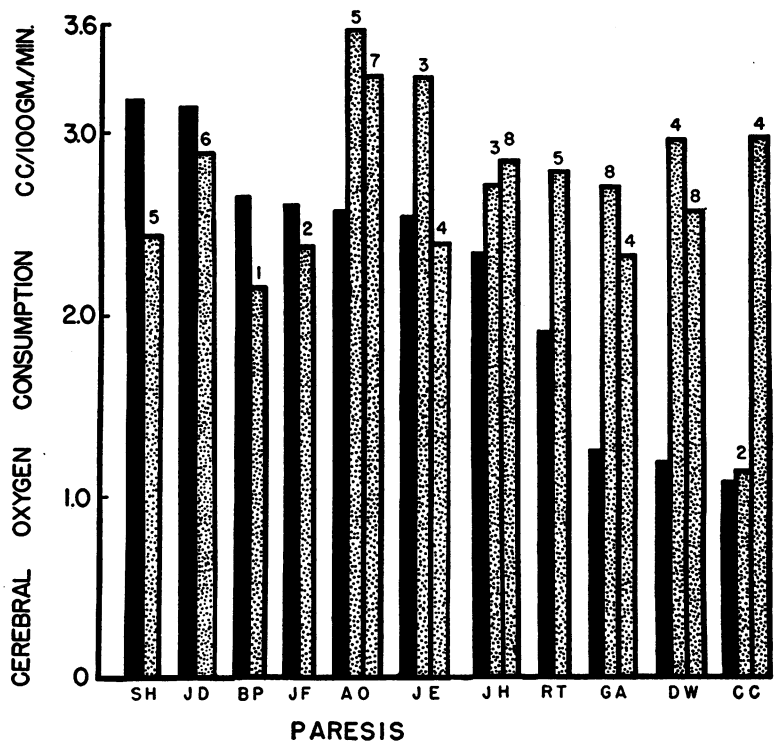

FIG. 3. THE EFFECT OF TREATMENT ON THE CEREBRAL OXYGEN CONSUMPTION IN PATIENTS WITH PARESIS

The solid columns represent the pre-treatment and the stippled columns the post-treatment determinations. The numbers above the columns indicate the interval in months between the determinations.

increase in $CMRO_2$, one showed no change, and one had a moderate decrease in oxygen consumption.

Figure 4 shows the changes in oxygen consumption in the first and second post-treatment studies plotted against the changes in blood flow observed at these times. The correlation between these changes was definite but of rather low order ($r = .68$). Several of the patients who had marked increases in oxygen consumption showed only minor changes in blood flow. In only one patient was there a definite decrease in CBF without a corresponding alteration in $CMRO_2$. It is evident that the changes in oxygen consumption were proportionately much greater than those in blood flow.

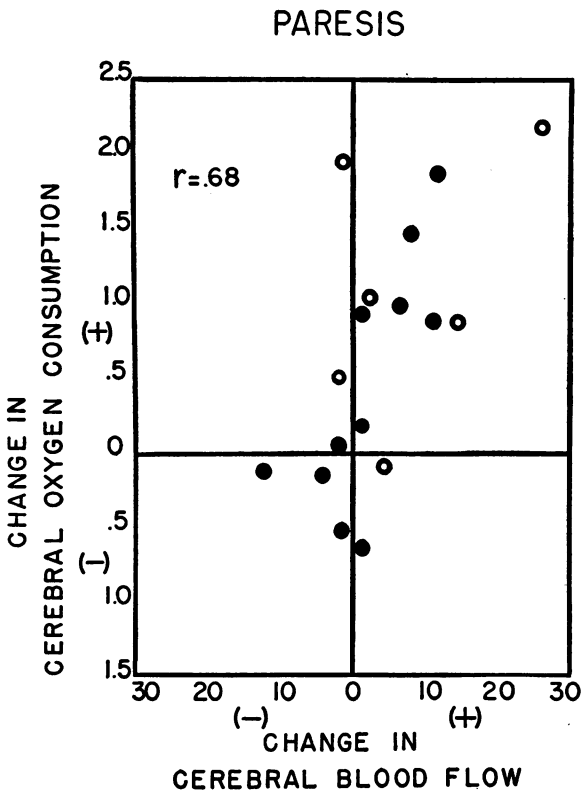

FIG. 4. CORRELATION BETWEEN CHANGES IN CEREBRAL BLOOD FLOW AND CHANGES IN CEREBRAL OXYGEN CONSUMPTION FOLLOWING TREATMENT OF PATIENTS WITH PARESIS

The numbers in the abscissa and ordinate indicate the change in cc. of blood and oxygen, respectively, per 100 Gm. brain/min. The solid dots represent the change observed in the first post-treatment determination, while the circles represent changes in the second post-treatment determination.

DISCUSSION

The decrease in cerebral blood flow observed in patients with dementia paralytica and meningovascular syphilis is consistent with the reduction in lumen of the cerebral vessels known to occur in these conditions. The cerebral blood flow, as determined by the nitrous oxide technique, represents principally the flow through *perfused* brain and does not account for cerebral tissue which is completely devoid of blood supply. If such tissue were taken into consideration, the CBF per unit of total brain substance might, in some individuals, be lower than that indicated by our study.

Patients with advanced dementia paralytica often show a considerable degree of cortical atrophy with a loss in brain substance, amounting to 100 Gm. or more (10). In such individuals. the reduction in total cerebral blood flow should be somewhat greater than that indicated by the reduction in flow per unit weight of brain. The total intracranial blood flow in dementia paralytica was indeed found to be reduced by Rosenbaum and his associates (2). These workers, however, could not be certain whether this diminution in flow was the result of a decrease in the cerebral vascular bed associated with decrease in brain volume or whether the blood flow per unit of brain substance was impaired. The results of our studies indicate that both factors may be operative.

The patients with asymptomatic neurosyphilis showed mean CBF and $CMRO_2$ values in the normal range. The average duration of syphilis was found to be less than nine years in the 12 patients in whom this factor could be determined. It seems probable that in most of these patients there were only minimal changes in the cerebral vessels and parenchyma, which were evidently insufficient to produce alterations in cerebral circulation and metabolism. There was a tendency for the patients with longer duration of neurosyphilis to have lower CBF values. Five of the seven patients with the lower blood flows were known to have had the disease for 10 years or more. The two patients with the lowest $CMRO_2$ values of 1.8 and 2 cc./100 Gm. brain/min. developed prompt relief of headaches and nervousness following penicillin treatment and may, in retrospect, have been cases of symptomatic, possibly early paretic, neurosyphilis.

The results of these studies have some bearing

on the problem of the pathogenesis of cortical atrophy in dementia paralytica. Merritt, Putnam and Campbell (11) have suggested that the degenerative changes in the cortex of the paretic brain are secondary to ischemia produced by disease of the cerebral vessels. The fact that the mean percentile reduction in blood flow before treatment in the patients with dementia paralytica was almost identical with that found in oxygen consumption (73 per cent vs. 72 per cent) may be evidence in support of this hypothesis. On the other hand, four patients showed considerable improvement in $CMRO_2$ and two others had a moderate decrease in $CMRO_2$ with very little or no change in cerebral blood flow. This dissociation of CBF and $CMRO_2$ suggests that disease of the cerebral vessels may not be the sole cause of changes in nerve cell function.

The nature and distribution of pathologic processes in the brain, as well as the overall rate of cerebral metabolism, appear to be important factors in determining alterations in mental function. A reduction of cerebral oxygen consumption to 2.0 cc./100 Gm./min. is usually associated with coma in patients with diabetic acidosis, insulin shock and brain tumor (12). In contrast, six of our patients had $CMRO_2$ values below this level and, although greatly deteriorated, these individuals were nevertheless conscious and capable of simple mental functions.

SUMMARY

1. The cerebral blood flow (CBF), oxygen consumption ($CMRO_2$), and vascular resistance (CVR) were determined by the nitrous oxide technique in 58 patients with neurosyphilis and 16 control subjects.

2. In patients with dementia paralytica and meningovascular syphilis the mean CBF and $CMRO_2$ were significantly reduced, while the mean CVR was significantly increased. In asymptomatic neurosyphilis these functions were within the normal range.

3. In patients with dementia paralytica, a definite correlation was found between the degree of mental deterioration and the reduction in cerebral oxygen consumption.

4. In patients with meningovascular syphilis, treatment was usually followed by a rise in CBF, while the $CMRO_2$ showed a variable response.

5. Treatment with penicillin and fever was followed by a rise in the $CMRO_2$ in those patients with dementia paralytica who had low pre-treatment values. This increase in $CMRO_2$ was accompanied by improvement in mental state.

ACKNOWLEDGMENT

We are indebted to Dr. Seymour S. Kety for instruction in the technique utilized in this paper and to Misses Mary McPhaul, Fransetta Vinson, Ann Payne, Voncile Williams, and Eloise Cavin for their technical assistance.

BIBLIOGRAPHY

1. Scheinker, I. M., Neuropathology in its Clinicopathologic Aspects. Charles C. Thomas, Springfield, Ill., 1947.
2. Rosenbaum, M., Roseman, E., Aring, C. D., and Ferris, E. B., Jr., Intracranial blood flow in dementia paralytica, cerebral atrophy and schizophrenia. Arch. Neurol. & Psychiat., 1942, **47**, 793.
3. Himwich, H. E., and Fazekas, F., The oxygen content of cerebral blood in patients with acute symptomatic psychoses and acute destructive brain lesions. Am. J. Psychiat., 1944, **100**, 648.
4. Wortis, J., Bowman, K. M., and Goldfarb, W., Human brain metabolism. Normal values and values in certain clinical states. Am. J. Psychiat., 1940, **97**, 552.
5. Kety, S. S., and Schmidt, C. F., The nitrous oxide method for the quantitative determinations of cerebral blood flow in man: theory, procedure and normal values. J. Clin. Invest., 1948, **27**, 476.
6. Orcutt, F. S., and Waters, R. M., A method for the determination of cyclopropane, ethylene, and nitrous oxide in the blood with the Van Slyke-Neill manometric apparatus. J. Biol. Chem., 1937, **117**, 509.
7. Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry, Vol. II, Methods. Williams & Wilkins, Baltimore, 1943. (Emended Editon.)
8. Kety, S. S., Harmel, M. H., Broomell, H. T., and Rhode, C. B., The solubility of nitrous oxide in blood and brain. J. Biol. Chem., 1948, **173**, 487.
9. Lennox, W. G., The cerebral circulation. XIV. The respiratory quotient of the brain and of the extremities in man. Arch. Neurol. & Psychiat., 1931, **26**, 719.
10. Merritt, H. H., Adams, R. D., and Solomon, H. C., Neurosyphilis. Oxford University Press, New York, 1946.
11. Merritt, H. H., Putnam, T. J., and Campbell, A. C. P., Pathogenesis of the cortical atrophy observed in dementia paralytica. Arch. Neurol. & Psychiat., 1937, **37**, 75.
12. Kety, S. S., Circulation and metabolism of the human brain in health and disease. Am. J. Med., 1950, **8**, 205.