Long Term Changes in Blood Pressure and Risk of Cerebrovascular Disease

SIMON W. RABKIN, M.D., F.R.C.P. (C), FRANCIS A. L. MATHEWSON, M.D., AND ROBERT B. TATE, M.SC.

SUMMARY Little attention has been given to assessing risk factors for cerebrovascular disease (CBVD) and less has been given to relating long term changes in blood pressure (BP) to CBVD occurrence. In the Manitoba Study a cohort of 3,983 North American men (predominantly between 25–34 years of age at entry in 1948), measured 5 times during the 26 year observation period from 1948 to 1974, was related to the incidence of CBVD. Used were measurements of age, systolic (SBP) and diastolic (DBP) blood pressure and Body Mass Index-weight/height determined at entry and at examination closest to July 1, 1954, 1959, 1964 and 1969. Change was calculated as the difference in these variables between examinations. In order to adjust for age and BP as CBVD risk factors, as well as for the effect both may have on the rate of BP change, the data were analyzed using multivariate as well as univariate methods.

After adjusting for age and SBP, change in SBP was significantly associated with subsequent CBVD, primarily in men middle aged or older. When considering SBP after entry, changes from a measurement 5 years earlier were more important than SBP changes over longer intervals. Thus, in evaluating SBP as a risk factor for CBVD, the rate of change in SBP is an also important factor in the identification of the stroke prone individual.

IDENTIFICATION of persons at high risk for development of a disease, is an important initial step in prevention of that disease. The search for factors which increase the risk of cerebrovascular disease (CBVD) is therefore highly relevant. The clinical observation that some persons manifest CBVD after a short period of rise in blood pressure to “hypertensive levels” raises the possibility that BP change may be a CBVD risk factor. To our knowledge this has not been previously investigated. The purpose of this report was to examine, in a prospective cardiovascular study, the hypothesis that the magnitude of BP change over time or the rate of change of BP is a predictor of the occurrence of CBVD.

Methods

Details of this Manitoba Study have been reported previously. In summary, the cohort consisted of 3,983 healthy men fit for pilot training in World War II. From 1946 to 1948 contact was re-established with the post-war survivors and on July 1, 1948, the Study population was sealed. For each subject measurements of age, blood pressure, body weight and height at the examination closest to June 30th, 1948 (date that population was defined) were selected as the entry examination. The mean age at entry was 30.8 years. Medical information and examinations provided evidence that they were without clinical manifestations of CBVD at entry. Since then, they have been followed by annual mail contact and periodic medical examinations. The observation period was defined from July 1, 1948 until June 30, 1974, an average follow up of 26 years. Annual contact has been lost with only 1 person.

Persons with secondary hypertension were not excluded from analysis because of their small number...
and because the objective of the Study was the relationship of blood pressure to CBVD regardless of the causes of elevated pressure. Also, persons prescribed antihypertensive medications were included in the analysis for several reasons: 1) their small numbers — less than 10% of highest BP group; 2) their presence only in later examinations; 3) problems in assessing their reliability or compliance (Sackett reported that compliance with long term medication regimens is only 54%); 4) in another population no effect on long term blood pressure changes from reported anti-hypertensive therapy could be found perhaps due to problems of compliance; 5) any effect of antihypertensive medications would make our conclusions conservative ones. However, information as to those groups prescribed antihypertensive medications is provided when relevant.

While systolic (SBP) and diastolic (DBP) blood pressures (BP) have been recorded during the observation period, SBP received more attention in the present analysis because: 1) the advantages of less error in measurement; 2) wider range of values; 3) it correlated with diastolic pressure; 4) it is more strongly associated with pathologic evidence of cerebral atherosclerosis; 5) it is of equal or better value as a risk factor for CVD; 6) it has been recommended for assessment of CBVD risk.

Diagnostic Criteria and CBVD Incidence

The criterion for CBVD was based on the description of the event and weighed according to the strength of the evidence. (See Appendix B). This approach was chosen because this cohort is not a community one in which all cases might undergo a standard investigation. Rather, it received reports from many different hospitals.

During the 26 year observation period 78 persons with CBVD were identified. Of these, 52 (67%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) had probable and 16 (21%) had definite, 10 (13%) 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The possibility of non-linear relationships between BP change and CBVD risk exists; that is, an increased risk may exist for large positive and large negative changes, or a sub-group of CBVD may exist with differing magnitude of SBP change. Therefore, a quadratic term for change was also included in the logistic function.

Another multivariate method that we used to assess the potential importance of blood pressure measurements after entry, was the approach of...
Truett and Sorlie. This method requires that all measurements at examinations prior to onset of CBVD be known as well as all measurements for the comparison group. In this cohort the majority of missing observations are in 1954. The low CBVD incidence in the early years resulted in only 3 CBVD cases occurring between 1954 and 1959 who had both previous measurements. Because of these two factors and in order to use this method, the 69 CBVD cases with all measurements in 1969, 1964 and 1959 were considered along with age in the last examination. Thus, blood pressure data are used at time periods 5, 10 and 15 years prior to the event. The hypothesis tested was that of an increasing difference in BP between the control group and CBVD group, with measurements closer to the event.

Results

Change in SBP, DBP and BMI for each of the 4 intervals is shown for entry ages 25 to 34 years, 35 to 44 years and greater than 44 years, in figures 1 to 3 respectively. Age group 15 to 24 years is not shown because only 1 person in that age group developed CBVD. For SBP the mean change was larger in the CBVD group compared to the no CBVD group in all intervals and age groups except for the first interval in those initially 25–34 years of age. Mean DBP change was larger in the CBVD group for all those less than 45 years at entry. Except for DBP in those 45 years or older at entry, the difference in SBP and DBP between the CBVD and no CBVD groups widened with increasing age both at entry and during the observation period. The results were the same or slightly more prominent in those whose evidence for CBVD was in the definite category.

The mean change in body weight shown at the bottom of figures 1 to 3 are similar in CBVD and no CBVD except for the later intervals in those initially 25–34 years of age. Also, of note is the negative weight change in the last 2 intervals for those over 44 years when SBP shows the most prominent positive change. BP change for all 4 intervals was classified according to BP levels at entry (figs. 4–5). In the no CBVD group those at a lower BP range initially showed a positive change in BP while those at higher BP range showed a fall in BP. Comparing the CBVD and no CBVD groups the mean change in SBP or DBP shows
The coefficients for age, SBP and SBP change calculated from 2 logistic functions in the 4 time intervals are shown in table 1. Change was found to be significantly associated with CBVD occurrence even after adjusting for the effects of SBP and age. Also, SBP change constituted an excess risk for CBVD. The relative risk\(^{19}\) (exponential of standardized coefficient) was greater than 1. The longer the interval the larger the standardized coefficients and relative risks for SBP change. The number of CBVD cases predicted for the logistic function was compared with the actual number observed for each decile of risk.

Because the importance of SBP change might be due to a change to a higher BP value closer to the CBVD event, the coefficients for the logistic functions relating to CBVD occurrence to age and SBP at examination at the end of each interval as well as SBP change are shown in table 2. Examining the function without a quadratic term for change, SBP change was significantly associated with CBVD occurrence with progressive increase in length of the interval. The function with the quadratic term shows the importance of SBP change for all the intervals. The correlation between the number of CBVD cases observed and the number predicted by the logistic function was good. For example, for the function without the quadratic term for change the correlation coefficients ranged from 0.970 to 0.983.

To determine if the decreasing significance of SBP change in the last 2 intervals was due to the increasing length of the interval or due to the particular years involved, 5 year changes were calculated for 1964 to 1969 and 1959 to 1964, and considered along with age and SBP at the end of the interval in the logistic functions. These 5 year changes were significantly\(^{19}\) (\(p < 0.01\)) associated with subsequent CBVD.

Using the method of Truett and Sorlie\(^{22}\) an increasing linear trend was found in the differences in systolic BP between the CBVD and no CBVD groups with repeated measurements closer to the event (table 4). The hypothesis of equality of the differences between the blood pressure of the 2 groups at different times prior to the event, that is, repeated measurements, have the same effect regardless of the time prior to the time the event was rejected (\(\chi^2 = 14.32, p < 0.01\)). The existence of increasing linear trend in the differences was significant (\(\chi^2 = 9.95, p < 0.01\)), thus indicating the advantage of repeated measurements, the ones closer to the event best distinguishing the 2 groups.

**Discussion**

Relatively little prospective data have been accumulated on CBVD. This has been in part due to the greater difficulty in diagnosis and its occurrence mainly in older age groups with a resulting smaller degree of premature morbidity.\(^4\) However, CBVD ranks second or third among the leading causes of death in many countries and is often responsible for severe disability in survivors.

In the identification of stroke-prone individuals advancing age is an extremely important but an unmodifiable factor.\(^1\)\(^*\) The most potent risk factor to emerge from the prospective epidemiologic study of stroke is blood pressure.\(^{13,23,24}\) In the present study, after adjusting for the effects of age and BP both at entry and at several examinations throughout the observation period, change in BP after entry was also a significant factor.

Several important cautions must be considered. Firstly, the Manitoba Study is a selected cohort and extrapolation to the general population must be done with caution even though there is concern that no epidemiologic study is representative of the general population.\(^{25}\) Secondly, survival to each examination during the observation period is itself a selective process. Thirdly, the lack of other CBVD risk factors...
is a concern. The significance of cholesterol as a CBVD risk factor is not settled. Pre-existing ischemic heart disease is an important risk factor but BP change in those with CBVD is greatly in excess of those with ischemic heart disease. The importance of BP change after consideration of other factors, such as cigarette smoking and hyperlipemia, in the present study is unknown and must await investigation by others. Next, there are hazards in relying on logistic function for analytic purposes, even though it is an excellent tool for predictive purposes. However, in the present study, examining the SBP change within age or blood pressure groups, supports the findings of the multivariate analysis. Next, it is difficult to prove with certainty that the importance of SBP change is due to change itself rather than change to a BP closer to the CBVD event. Regardless, the concept of BP change is important. For epidemiologic studies that rely only on the entry BP, the present investigation showed that BP change to later values is a significant factor. For those who are assessing a man’s CBVD risk we suggest that BP change from a value 5 years earlier is also a significant consideration. Lastly, the variability of repeated casual BP measurements is well known. This study examined groups of individuals which minimizes the variability.

The concept that BP change may be associated with CBVD is not new. Evelyn reported several cases where “the transition from the normotensive to the hypertensive state is abrupt and the disease tends to develop in a severe and rapidly progressive form” which can terminate with a cerebrovascular accident. Farmer et al. noted that a shorter known duration of hypertension or a greater rate of change to hypertensive levels was associated with a higher mortality rate, the majority of which deaths was due to CBVD. Case reports and retrospective evidence, while important, have the potential problems of bias in case selection and difficulties in defining with precision the onset of “hypertension”. Prospective or longitudinal studies are best able to examine the change in blood pressure over time. Such studies have focused their attention on describing the change and factors associated with it. We have observed an association between BP change and the occurrence of ischemic heart disease and Oberman et al. found that change in SBP was an important predictor of radiologic evidence of cardiomegaly. We are not aware of any other epidemiologic study which has examined the relationship between BP change and CBVD risk.
Whether the increased risk associated with BP change is a manifestation of already damaged vasculature, or is a direct cause of CBVD is uncertain. Speculation on a noncausal relationship must consider the possibility that a factor such an increased renin or angiotension may result in both a greater rate of change in BP as well as damage to the vascular wall, thus accelerating the development of clinical complications of cerebral atherosclerosis. However, a causal relationship between BP change and CBVD is possible. Interpreting this in the light of some theories of atherosclerosis, BP change may either alter endothelial permeability or represent damage to vascular endothelium or increase stretch on the artery, each of which may allow entry of more lipid into the arterial wall, accelerating the development of cerebral atherosclerosis.

### Table 1: Logistic Function Coefficients and Standardized Coefficients Relating to CBVD Occurrence in Several Observation Periods, Age and SBP at Entry and Change (Δ) in SBP from Entry to Beginning of Observation Period

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<tbody>
<tr>
<td>Age at entry</td>
<td>0.180**</td>
<td>0.178**</td>
<td>0.161**</td>
<td>0.156**</td>
<td>-18.86</td>
</tr>
<tr>
<td>SBP at entry</td>
<td>1.144</td>
<td>1.131</td>
<td>1.015</td>
<td>1.003</td>
<td>-17.184</td>
</tr>
<tr>
<td>Δ SBP from entry to beginning of observation period</td>
<td>0.068**</td>
<td>0.052**</td>
<td>0.068**</td>
<td>0.061**</td>
<td>-18.318</td>
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<td>Δ SBP from entry to beginning of observation period</td>
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<td>0.533</td>
<td>0.714</td>
<td>0.645</td>
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</table>

For each variable the logistic function coefficient is shown first and below it the standardized coefficient. For each observation period the results with and without a quadratic (Δ^2) term for SBP change are shown in the first and second columns respectively. Relative risk is the exponential of standardized coefficient, e.g. for SBP change from 1948 to 1969 it is 4.2.
TABLE 2  Logistic Function Coefficients and Standardized Coefficients Relating to CBVD Occurrence in Several Observation Periods, Age and SBP at Beginning of Observation Period as Well as Change (Δ) in SBP from Entry to Beginning of Observation Period

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<tr>
<td>Age at beginning of observation period</td>
<td>0.178**</td>
<td>0.176**</td>
<td>0.154**</td>
<td>0.162**</td>
<td>0.156**</td>
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<tr>
<td>SBP at beginning of observation period</td>
<td>1.124</td>
<td>1.112</td>
<td>0.954</td>
<td>0.940</td>
<td>0.929</td>
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<tr>
<td>Δ SBP from entry to beginning of observation period</td>
<td>0.067**</td>
<td>0.050**</td>
<td>0.070**</td>
<td>0.064**</td>
<td>0.100**</td>
</tr>
<tr>
<td>Δ² SBP</td>
<td>-0.032*</td>
<td>-0.038**</td>
<td>-0.024*</td>
<td>-0.027*</td>
<td>-0.025†</td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.00146**</td>
<td>0.00045†</td>
<td>0.00099**</td>
<td>0.00193**</td>
<td></td>
</tr>
</tbody>
</table>

Number of cases: CBVD/No CBVD 62/3511 70/3804 57/3712 36/3615

For each variable the logistic function is shown first and below it the standardized coefficient. For each observation period the results with and without a quadratic (Δ²) term for SBP change are shown in the first and second columns respectively.

TABLE 3  Logistic Function Coefficients and Standardized Coefficients Relating Age and SBP in 1964 and 1969 as Well as 5 Year SBP Change to CBVD Occurrence in the Observation Period Which Followed

<table>
<thead>
<tr>
<th>Observation period</th>
<th>Variable</th>
<th>1964 to 1974</th>
<th>1969 to 1974</th>
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</thead>
<tbody>
<tr>
<td>Age at beginning of observation period</td>
<td>0.150**</td>
<td>0.132**</td>
<td>0.131**</td>
</tr>
<tr>
<td>SBP at beginning of observation period</td>
<td>0.092**</td>
<td>0.101**</td>
<td>0.089**</td>
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<tr>
<td>5 year Δ SBP</td>
<td>-0.022†</td>
<td>-0.019†</td>
<td>-0.041**</td>
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<tr>
<td>5 year Δ² SBP</td>
<td>0.000601*</td>
<td>0.000732*</td>
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</table>

Number of cases: CBVD/No CBVD 57/3703 36/3606

For each variable, the logistic coefficient is shown above and the standardized coefficient below. 5 year Δ SBP in the second column is for the interval 1959 to 1964 and in the third column for 1964 to 1969.

TABLE 4-A  Mean SBP for CBVD and No CBVD Cases

<table>
<thead>
<tr>
<th>Last examination prior to CBVD onset</th>
<th>Examinations at which blood pressures were measured</th>
<th>Number of men</th>
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</thead>
<tbody>
<tr>
<td>1964</td>
<td>135.7</td>
<td>15</td>
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<tr>
<td>1969</td>
<td>140.8</td>
<td>22</td>
</tr>
<tr>
<td>1974</td>
<td>135.6</td>
<td>32</td>
</tr>
<tr>
<td>No CBVD</td>
<td>124.3</td>
<td>3599</td>
</tr>
</tbody>
</table>

TABLE 4-B  Difference in Mean SBP for CBVD and No CBVD Cases

<table>
<thead>
<tr>
<th>Last examination prior to CBVD onset</th>
<th>Examinations at which blood pressures were measured</th>
<th>1969</th>
<th>1964</th>
<th>1969</th>
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</thead>
<tbody>
<tr>
<td>1964</td>
<td>11.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1969</td>
<td>16.5</td>
<td>29.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1974</td>
<td>11.3</td>
<td>17.7</td>
<td>21.2</td>
<td></td>
</tr>
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</table>

sclerosis. Also to be considered is that change in BP may be responsible for lesions in small cerebral vessels which may play a role in CBVD.37

When relating BP change to BP at the end of the interval, the function with the quadratic term was a better one for the assessment of an association with CBVD. For earlier time periods this was most likely due to the sub-group of CBVD who showed a negative change in BP from a previously higher reading. This is consistent with the observation that "transient hypertensive readings" increase the risk of cardiovascular-renal disease and death.38 In the later intervals, non-linearity may be due to the wide range of BP change in the CBVD group.

In conclusion, the concept of SBP change is important in the identification of the stroke-prone individual. It raises intriguing questions concerning the pathogenesis of CBVD and whether a further reduction in incidence of CBVD could be obtained if SBP change were considered as a factor in the treatment of hypertension.
Acknowledgment

We wish sincerely to thank the 3,983 members of the Study group, whose outstanding cooperation has made the collection of these data possible. The success of the follow up program is due to the efforts of Mrs. A. R. Scott and Mr. C. M. Leslie and the support staff. We also thank Dr. A. H. Harrop, Mrs. E. Thomas, Ms. S. Prosick, Ms. J. Neufeld for preparation of the manuscript and Dr. R. T. Ross for his critical reviews of this manuscript.

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Appendix A

In the logistic model, CBVD risk (R) or probability of CBVD is the followup period is represented by the equation

\[ R = \frac{1}{1 + e^{-(B_0 + B_1 X_1 + \ldots + B_n X_n)}} \]

where \( B_0 \) is the intercept, \( B_1, B_2, \ldots, B_n \) are the logistic function coefficients estimated from data consist of CBVD status at a specific time and measured levels for K risk factors \( X_1, X_2, \ldots, X_n \).

In the logistic function the coefficient for BP change has negative sign when it is considered with BP at the end of the time interval. While at first glance this suggests a positive change in BP will reduce the risk of CBVD, that is not the real meaning. The SBI measurement at entry \( X_1 \) and the SBI at the end of interval \( X_2 \) are both positively associated with incidence of CBVD. Because SBI at the end of the interval has a stronger association with CBVD, the general form of the exponent of the logistic function at fixed levels of all variables other than \( X_1 \) and \( X_2 \) will be

\[ K + A X_1 + (A+B) X_2 \]

Where K is a constant determinant by the intercept and value at fixed levels of the other variables

\[ A > 0 \text{ is the coefficient for } X_1 \]

\[ A + B, B > 0 \text{ is the coefficient for } X_2 \]
Thus, for variables \( X_2 \) and \( X_2 - X_1 \), in the logistic function the general form will be as follows:

\[
K + AX_2 + (A + B)X_2 = k + AX_2 + (A + B)X_2 - AX_2 \\
= k + (2A + B)X_2 - (A)(X_2 - X_1)
\]

coefficient for \( X_2 \), \((2A + B)\) is positive
coefficient for \( X_2 - X_1 \), \(-A\) is negative

### Appendix B

### Diagnostic Criteria for CBVD

#### Definite

1. Stroke: when all 3 of the following criteria are met:
   
   I. One or more of the following symptoms and/or signs:
   
   a) Carotid-cerebral arterial system: weakness or numbness in the contralateral limbs (arm, leg or both), homonymous or monocular visual loss, dysphasia or agnosia.
   
   b) Vertebral-basilar arterial system: weakness or numbness of one or more limbs; episodes of vertigo and nausea; numbness of the face, particularly about the mouth; diplopia, dysphagia; dysarthrias; homonymous hemianopsia; ataxia; nystagmus or altered consciousness.
   
   II. The above symptoms or signs for more than 24 hours.
   
   III. Objective neurological deficits are present.
   
   (Events due to another known cause, for example, trauma, were excluded.)

2. Intermittent Cerebral Ischemic Attacks (ICIA); when all 3 of the following criteria are met:
   
   I. One or more of the above symptoms and/or signs were present with sign(s) confirmed by physician’s observations:
   
   II. The symptoms or signs persist for less than 24 hours.
   
   III. There are repetitive episodes.

3. Death from Stroke.

#### Probable

1. Stroke — when one or more of the above signs or symptoms were present but were equivocal, persisted for more than 24 hours, and equivocal neurological deficits or residua were present.

2. ICIA — When one or more symptoms were reported by the patient and there were no neurological signs confirmed by the physician’s observations or there were episodes of vertigo or altered consciousness where no attempt has been made to exclude other causes.

#### Reported

Stroke or ICIA reported by physician but no documentation of clinical event available.

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### Effects of Phenobarbital in Cerebral Ischemia

#### Part I: Cerebral Energy Metabolism During Pronounced Incomplete Ischemia

**CARL-HENRIK NORDSTRÖM, M.D., AND BO K. SIESJÖ, M.D.**

**SUMMARY** Changes in cerebral cortex concentrations of high-energy phosphates, glycolytic metabolites, citric acid cycle intermediates, associated amino acids, and ammonia, were studied after 5, 15 and 30 min of incomplete ischemia in rats anesthetized with 70% N₂O or 150 mg·kg⁻¹ of phenobarbital. Previous results have shown that with this type of ischemia (bilateral carotid artery occlusion combined with reduction in blood pressure to 50 mm Hg) cortical blood flow is reduced to below 10% of nitrous oxide control values, whether animals are anesthetized with 70% N₂O or 150 mg·kg⁻¹ of phenobarbital.

In animals under 70% N₂O, changes in tissue concentrations of phosphocreatine, ATP, ADP and AMP were similar to those previously obtained in complete ischemia. However, some glucose remained in the tissue, and the lactate concentrations gradually rose to reach excessive values. Changes occurring in glycolytic and citric acid cycle intermediates were similar to those seen in complete ischemia but, after 30 min, there was some reduction in the pool size of amino acids.

In those animals given phenobarbital and which lost all EEG activity during ischemia, changes in cerebral metabolites were virtually identical to those observed in nitrous oxide-anesthetized animals. However, some animals exposed to 5 or 15 min of ischemia had some remaining EEG activity. In these, cerebral energy state was significantly less deranged, and levels of glycogen, glucose and pyruvate were higher.

ALTHOUGH brain damage has been reported after cardiac arrest of only 4-5 min duration and although the first signs of histological damage may be detected following a 5-10 min period of hypoxia-ischemia, other observations indicate that remarkable functional and biochemical restitution is possible after prolonged periods of complete cerebral ischemia.

It has been argued that the barbiturate anesthesia used in many of these experiments may have ameliorated the brain damage. However, in a previous communication from this laboratory we described near-complete recovery of cerebral energy metabolism, following 30 min of complete ischemia in rats under 70% N₂O, and the pattern of changes in high-energy phosphates, carbohydrate metabolites and amino acids was the same in animals anesthetized with nitrous oxide and phenobarbital.

It was reported by Hossmann and Kleihues that if the cerebral ischemia was incomplete, i.e. if there was a trickling flow during the ischemic period, recovery
Long term changes in blood pressure and risk of cerebrovascular disease.
S W Rabkin, F A Mathewson and R B Tate

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