NERVOUS DISORDER IN ACUTE CARBON MONOXIDE POISONING

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In acute carbon monoxide poisoning the action of carbon monoxide on living organism has not been recognized to be explained satisfactory on the basis of oxygen lack alone, and thus some factors which might explain the essential properties of carbon monoxide poisoning have been assumed and investigated. We have found a factor by examining animals exposed to carbon monoxide biochemically and pharmacologically. The factor in acute carbon monoxide poisoning was the velocity of carboxyhemoglobin formation, but not carboxyhemoglobin formation in itself. This factor may be named as the inner circumstance factor corresponding to the outer circumstance factor. This factor may also be considered to have some important roles not only in carbon monoxide poisoning but also in other many poisonings.

In spite of the efforts of many investigators, three important problems in clarifying the essential properties of the carbon monoxide poisoning have remained. The first is the problem about the mechanism of acute and chronic poisoning. It has not yet been clarified whether or not the mechanism of chronic poisoning caused by long term exposure to small concentrations of carbon monoxide was fundamentally different from that of acute poisoning being due to short term exposure to large concentrations.

The second is the problem about the brain damage observed in acute poisoning. The brain damage has been assumed to be caused by the preventive effect of carboxyhemoglobin on the transport of oxygen to brain tissues. It is well known that the most sensitive organ to anoxia is the brain\(^1\), since it consumes the largest proportion of oxygen of the whole organism. The cerebral cortex and the globus pallidus might be usually supposed to be most sensitive to hypoxia\(^2\), but in fact, numerous studies of anoxic lesions of the encephalon have shown that the most important damage in the brain was the demyelination or a diffuse necrosis of the white matter. Shiraki\(^3\) et al have reported that the lesions of the white matter were usually observed in acute carbon monoxide, and in some cases, the lesions of the globus pallidus and cerebral cortex together with the pulmonary oedema occurred. However, there is no general agreement that the white matter is more susceptible to carbon monoxide than the cerebral cortex. Some other biochemical signs together with the anatomical pictures are necessary to obtain a further com-
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plete topography of cerebral lesion in the poisoning. At present, however, investigations about the metabolic pattern in the brain of poisoned animals or persons have been scarcely published.

The third problem is a possible direct action of carbon monoxide on brain tissues. Besides anoxia, though according to Yamamura et al suppressed blood circulation to the brain causes the lesions of the white matter as in the case of carbon monoxide poisoning, many other factors may concern with the occurrence of the poisoning simultaneously or successively. Some people have supposed the inhibition of cytochrome oxidase activity by carbon monoxide of relatively high concentrations. Investigations about these factors should also be performed for clarifying the essential properties of carbon monoxide poisoning.

This study describes the changes of the amount of lactate, ATP, creatine phosphate, inorganic phosphate, ammonia and glutamine in the brain of animals exposed to various concentrations of carbon monoxide. Then, the reactivity against d-tubocurarine, which is an effective agent for cut off the neuromuscular junctions, were examined by using rabbits before and after the exposure. Finally, the changes of lipid content in the white and the gray matter by the exposure were investigated. These results were discussed in comparison with those obtained by the examination of animals exposed to low oxygen air.

MATERIALS AND METHODS

Experimental animals

The amounts of lactate, ATP, creatine phosphate, inorganic phosphate, ammonia and glutamine in the brain were determined by using Hartree guinea pigs weighing from 300 to 400 g. For d-tubocurarine test and for the determination of lipids in the brain, rabbits were used, especially for lipids determination litter rabbits were used. All animals were bred in a room of 24±1°C and 55±5% of humidity.

Apparatus for exposure

Into a polyethylene box of 40×23×23 cm³, in which animals were put, air containing carbon monoxide of various concentrations was introduced at a flow velocity of 5–6 l per min. The air was prepared by mixing carbon monoxide gas and air. Low oxygen air was obtained by diluting air with nitrogen gas.

Carboxyhemoglobin in the blood

The amount of carboxyhemoglobin formed in the blood was determined according to the method reported by Kampen et al

Determination of lactate, creatine phosphate, ATP, inorganic phosphate, ammonia and glutamine in the brain of guinea pigs

The head of guinea pig was cut off and put into liquid nitrogen for about 3 min. Then, brain tissues were removed and then powdered. One gram of the powdered tissue was homogenized with 2 ml of 0.6 M perchloric acid solution by
using a Waring blender, and the supernatant obtained by centrifuging at 11000 \( \times \) g for 5 min was used for the determination of various substances.

1) Lactate, creatine phosphate and ATP in the supernatant solution. The amounts of lactate and ATP were determined by using test-combination kits purchased from C. F. Boehringer Co. The determination of creatine phosphate was also carried out enzymatically by using the reagents of Boehringer Co. The amount of creatine phosphate contained in 0.1 ml of the sample solution was determined by measuring the increase of optical density being due to the formation of NADPH after mixing with ADP, creatine phosphokinase, glucose, hexokinase and NADP.

2) Determination of ammonia and glutamine. The amounts of ammonia and glutamine contained in the sample were determined by Conway's micro-diffusion method.

3) Determination of inorganic phosphate. The amount of inorganic phosphate was determined by Allen's method.

Head-drop test of rabbit by d-tubocurarine

Head-drop test by d-tubocurarine was used for estimating the effect of carbon monoxide on the nervous system by measuring the amount of d-tubocurarine required for head-drop of rabbit before and after the exposure. The details of the procedure were described already in a previous paper.

Determination of phospholipid and cholesterol in brain tissues

1) Extraction and separation procedures of phospholipid and cholesterol. Brain tissues removed from the skull immediately after killing by introducing air into the vein were separated to the white and the gray matter on a glass plate placed on ice. Perfect separation of all tissues is not necessarily, because only 0.5 g of each of the matters are used for the determination, and thus for this purpose, the contamination of both matters must be carefully to prevent. Five hundred milligrams of the white or the gray matter in 20 ml of a mixed solution of chloroform and methanol (chloroform : methanol = 2 : 1 v/v) were homogenized by using a Waring blender for 1 min. The homogenate was shaken mechanically for 1 hr, and then filtered through Toyo filter paper No. 51. After the filtrate was mixed with 4 ml of 0.1 M potassium chloride solution, it was stood over night to separate into two layers. The upper layer was removed off, and the lower was washed gently three times with the supernatant solution of a mixed solution of chloroform, methanol and 0.1 M potassium chloride (8 : 4 : 3). Then, the solvent of the lower layer was evaporated off at a decreased pressure within a possibly short time, and the residue was again dissolved in chloroform. After repeating the procedures of evaporation and dissolution three times, undissolved particles in the chloroform solution were finally filtered off, and then chloroform was evaporated off. The final residue dissolved into a small volume of chloroform was used for the determination of phospholipid and cholesterol.
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All of the sample solution were separated into several fractions on a silica gel G plate (250 µ) according to the techniques of thin layer chromatography. The developing solvent used was a mixed solution of chloroform, methanol and conc. ammonia (17 : 7 : 1)\textsuperscript{16}. After developing for 60 min, the plate was dried at room temperature. The fractions of phospholipid and cholesterol were marked by spraying with an ethanol solution containing 0.2% 2', 7'-dichlorofluorescein under an ultraviolet lamp. Qualitative ascertainment of each phospholipid fraction was carried out by comparing with the chromatographic behavior of pure materials of phospholipids, and further by coloring with special reagents such as ninhydrin\textsuperscript{17} reagents for phosphoethanolamine and phosphatidylserine, dragendorff reagents\textsuperscript{17} for phosphatidylcholine and sphingomyelin. Each fraction on the plate was collected respectively into test tubes.

2) Determination of phospholipid. Phospholipid of each fraction collected separately was decomposed into inorganic phosphate by heating on an electric furnaces for 3 hr after the addition of 0.4 ml of 70% perchloric acid. Then, the amount of inorganic phosphate was determined according to Wagner's method\textsuperscript{18} as follows. Two milliliters of water were added to the decomposed sample, and it was again heated for 10 min at 100°C. After cooling, it was colored with 0.3 ml of 2.5% ammonium molybdate and 0.3 ml of 10% ascorbic acid solution by incubating for 2 hr at 38°C. The optical density of colored sample was measured at 820 m\textmu after centrifuging to remove off the precipitate. The amount of each phospholipid was expressed as the amount of inorganic phosphate per gram of the tissue (mgP/g of wet weight of the tissue).

3) Determination of cholesterol. The cholesterol fraction separated from the plate was shaken with 3 ml of chloroform, and then the precipitate was filtered off. After evaporating chloroform off, the residue was colored with 3 ml of 0.08% ferric chloride\textsuperscript{19} in acetic acid and 2 ml of concentrated sulfuric acid by shaking vigorously for 1 min. After standing for 30 min the optical density of colored sample was measured at 560 m\textmu.

RESULTS

Changes of the amount of lactate, creatine phosphate, inorganic phosphate, ATP, ammonia and glutamine in the brain of guinea pigs exposed to carbon monoxide

The heads of guinea pigs exposed to various concentrations of carbon monoxide for 30 min were cut down to determine the amounts of lactate, creatine phosphate, inorganic phosphate, ATP, ammonia and glutamine contained in brain tissues. Simultaneously the amount of carboxyhemoglobin in the blood was determined. The concentrations of carbon monoxide used were 0.00, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30 and 0.50%. Three animals were used for every concentration of carbon monoxide. The amount of carboxyhemoglobin formed in the blood by the exposure to the above various concentrations of carbon monoxide was about 0, 8, 17, 25, 33-36, 40,
48-50 and 55-59% respectively. In each experiment, the amount of carboxyhemoglobin increased linearly for at least 30 min after the beginning of the exposure.

The exposure to carbon monoxide caused significant changes of metabolic pattern in brain tissues, especially the change of lactate metabolism. The marked effect of carbon monoxide on the amount of lactate in the brain was shown in Fig. 1 in correlation with the concentration of carboxyhemoglobin. As seen from the figure, the amount of lactate showed a rapid and sigmoid type increase with the concentration of carboxyhemoglobin.

Ginea pigs were exposed to various concentrations of carbon monoxide for 30 min, and then killed. The results in Figs. 1-6 were obtained by using the same animals.
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centratiion of carboxyhemoglobin after keeping the normal level until 20% of carboxyhemoglobin and then reached to the maximum, at which lactate concentration was over about three times larger than the normal, at 50% of carboxyhemoglobin.

The change of creatine phosphate was also fairly remarkable, though it was not so significant as that of lactate. As shown in Fig. 2, the amount of creatine phosphate began to decrease when carboxyhemoglobin concentration became over 20%. At 60% of carboxyhemoglobin it was about a half of the normal.

Fig. 3. Inorganic phosphate in brain tissues.

Fig. 4. Ammonia in brain tissues.
The amount of inorganic phosphate showed slow decrease till about 40% of carboxyhemoglobin content, and then rapid increase took place as shown in Fig. 3.

The change of ammonia seemed to consist of three phases: slow increase till 15-20% of carboxyhemoglobin, slow decrease from 20 to 30% carboxyhemoglobin and then fairly large increase shown over 30%. The change of glutamine showed similar phases as that of ammonia. These results were shown in Figs. 4 and 5.

The change of ATP by carbon monoxide intoxication showed no clear phase, although ATP content seemed to be fairly disturbed comparing with the normal (Fig. 6).
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By summarizing the above results, when carboxyhemoglobin content of the blood reached to 20% and further increased beyond the value, the metabolic pattern in brain tissues might be considered to take a disturbed state, at which some metabolites would keep their normal states and some other metabolites would take disturbed ways. According to Sayers20) the symptoms of acute carbon monoxide poisoning in man concerns with carboxyhemoglobin content, that is, tightness across forehead at 10-20% carboxyhemoglobin, headache and throbbing in temples at 20-30%, severe headache, dizziness and nausea at 30-40%, increase of pulse or respiration at 40-50% and Chenye-Stokes respiration and coma at over 50%.

The results obtained by animal experiments may be difficult to apply to men because of the differences in brain structure or of the vascularity differences in the brain3,4). However, the fact that the marked effect of carbon monoxide on lactate accumulation in the brain appears at over 20% of carboxyhemoglobin content may give some suggestions to explain the relationship between the symptoms and carboxyhemoglobin content in poisoned men.

Lactate content in the brain of guinea pigs which breathed low oxygen air

By taking into consideration both the decreased oxygen supply according to the formation of carboxyhemoglobin and the lactate accumulation in the brain, anoxic anoxia seems to be the essential factor of acute carbon monoxide poisoning, and thus metabolic disturbance in the brain, especially lactate accumulation, may be expected in animals exposed to low oxygen air.

In Fig. 7, the change of lactate content in the brain of guinea pigs caused by

![Graph showing lactate content in the brain of guinea pigs caused by breathing low oxygen air.](image)

Fig. 7. Change of lactate content in the brain caused by breathing low oxygen air.

Guinea pigs were breathed low oxygen air for 3 hours and then killed for determining the amount of lactate in the brain.
breathing air containing various concentrations of oxygen for 3 hr was indicated. At oxygen contents below 16% the amount of lactate in the brain increased slowly with the decrease of oxygen content as shown in the figure. The value of fractional oxygen saturation of arterial blood caused by breathing low oxygen air of 12% is about 73%21), which corresponds to the oxygen content of arterial blood at 25% of carboxyhemoglobin.

Oxygen supply to the brain is necessary to take account of the rate of O₂ use, blood flow, arterial and venous oxygen content and oxygen dissociation curve, and therefore it can not be assumed only from the values of fractional oxygen saturation of arterial blood.

The respiration of air containing below 8% of oxygen has been assumed to be dangerous to life22). Even in this case, however, the accumulation of lactate in the brain seemed to be rather smaller than expected. It may be recognized that oxygen lack does not cause any significant effect on the accumulation of lactate in the brain.

Effect of carboxyhemoglobin formation velocity on lactate accumulation in the brain

The accumulation of lactate in the brain caused by carbon monoxid intoxication was supposed as the result by unknown factors rather than oxygen deficiency. A possible factor may be carbon monoxide itself. Furthermore, the velocity of carboxyhemoglobin formation may be also effective factor, because the state of oxygen lack induced rapidly may be more effective to living organisms than that induced slowly. The velocity of carboxyhemoglobin formation in the blood may be therefore an important indicator for the velocity of inner state change.

In the experiments, guinea pigs were exposed to 0.1-1.0% of carbon monoxide and then killed when the carboxyhemoglobin content of the blood reached 46.5%. In Table 1, the amount of lactate contained in brain tissues was indicated against the time which was necessary for forming 46.5% carboxyhemoglobin. As seen

<table>
<thead>
<tr>
<th>Concentration of carbon monoxide (%)</th>
<th>Duration of exposure (min)</th>
<th>Lactate content in brain tissues (μmol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>160</td>
<td>4.66</td>
</tr>
<tr>
<td>0.1</td>
<td>50</td>
<td>4.88</td>
</tr>
<tr>
<td>0.2</td>
<td>25</td>
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<td>10</td>
<td>10.6</td>
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<tr>
<td>1.0</td>
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<td>10.6</td>
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Table 1. Relationship between lactate content in the brain and the velocity of carboxyhemoglobin formation in the blood.
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from the table, though the concentration of carboxyhemoglobin was nearly equal in all animals experimented, lactate content showed a considerable difference. For example, the increase of lactate content caused by exposure to 0.1% carbon monoxide for 160 min was negligible, while that caused by exposure to 0.2% carbon monoxide for 50 min was remarkable. Therefore, lactate accumulation caused by carbon monoxide exposure seems to occur proportionally to carbon monoxide concentration.

This finding may indicate the effectiveness of the velocity of inner state change in living organism on metabolic patterns in brain tissues. This factor would be named as "inner circumstance factor". The effectiveness of the factor depends on the velocity of the change and not on the change itself. The inner state change in acute carbon monoxide poisoning might be supposed as oxygen lack by carboxyhemoglobin formation, and therefore when the state of oxygen lack was induced slowly into brain metabolism, the metabolism, at least as far as on lactate metabolism, would proceed in the normal pattern, while rapid oxygen lack would cause serious changes of metabolic pattern.

In acute carbon monoxide poisoning, this effective factor should be taken into account, although only the amount of carboxyhemoglobin has been noticed until recently. Similar findings were obtained by Hornbein, Roos and Griffo in cases of anoxic test.

Tubocurarine test of rabbits exposed to carbon monoxide or low oxygen air

After exposing to various concentrations of carbon monoxide or low oxygen air for 6 hr, the reactivity of rabbits against d-tubocurarine, which acts on the neuromuscular junctions and cuts off the junctions which results in head-drop, was examined. The results were shown in Figs. 8 and 9. As seen from the figures, the necessary amount of d-tubocurarine for head-drop decreased by the exposure to carbon monoxide or low oxygen air, then it recovered to the normal level. The decrease was proportional to the concentration of carbon monoxide or reversibly proportional to oxygen content in air. In the case of carbon monoxide intoxication, the recovery process sometimes was not complete, that is, complete recovery was observed below 0.01% carbon monoxide, and beyond 0.03% it was not complete even after about one week of the exposure. In the case of low oxygen air, on the contrary, complete recovery was observed within one day after the exposure, whereas the decrease was nearly the same order as carbon monoxide poisoning immediately after the exposure.

The difference observed between carbon monoxide poisoning and low oxygen air breathing seems to indicate that many unknown factors, not to mention oxygen lack, act in the occurrence of carbon monoxide poisoning, sometimes cooperatively, and sometimes independently.
Phospholipid and cholesterol in brain tissues

By the exposure to carbon monoxide, nearly irreversible damage of nervous system was assumed to be caused, although the details of the damage such as the location or the degree of the damage could not be clarified by the head-drop test.

Fig. 8. Effect of carbon monoxide on d-tubocurarine susceptibility of rabbits.

d-Tubocurarine solution was introduced into animals through the ear vein until head-drop, and the total amount of the solution (ml) introduced was measured. In the figure, tubocurarine amount after the exposure was compared with that before the exposure. All rabbits were exposed to carbon monoxide for 6 hr.

Fig. 9. Change of tubocurarine susceptibility of rabbits caused by breathing low oxygen air.

All rabbits were breathed low oxygen air for 6 hr.
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According to pathological examinations of brain tissues of man in acute carbon monoxide poisoning, the lesions of the white matter such as demyelination was of most important and there appeared sometimes the lesions of the globus pallidus and the gray matter\(^3,4\). According to Yamamura\(^4\), the demyelination occurs by disturbing the blood flow to the brain in monkeys but scarcely in rats or rabbits. Shiraki et al\(^3\) reported that the lesions of the white matter of man were observed in cases of death which occurred within one or two days after the exposure to carbon monoxide, and it seemed to progress with time after the exposure. Marked demyelination was observed in a case of death which occurred at 40 days after the exposure.

In consideration of these anatomical findings in spite of Yamamura's\(^4\) report, it may be possible that lipid content in brain tissues of rabbits, especially in the white matter, shows some changes after the exposure.

Litter rabbits were exposed to 0.4% carbon monoxide for 30 min until about 50% of carboxyhemoglobin were formed and then continuously exposed to 0.06% carbon monoxide for 5.5 hr. Rabbits were killed immediately after the exposure, after 24 hr and 7 days, respectively, and the amounts of phospholipid and cholesterol in the white and the gray matter were examined. The results were shown in

![Diagram](image)

Fig. 10. Phospholipid content of brain tissues of rabbits exposed to carbon monoxide for 6 hr.

Rabbits of litter were exposed to 0.4% carbon monoxide for 30 min and then 0.06% carbon monoxide for 5.5 hr. Carboxyhemoglobin content of the blood was nearly 50% in all animals. Figs. 10 and 12 show the results obtained from the same rabbits.

PC: Phosphatidylcoline, PE: Phosphatidylethanolamine, PS: Phosphatidylserine, SPM: Sphingomyelin
Figs. 10, 11 and 12. In the gray matter, the amounts of phospholipid and cholesterol determined immediately after the exposure showed some decreases in comparison with their normal values, respectively, and then almost recovered within 24 hr. Thereafter they kept the normal values. In the white matter, on the other hand, phospholipid content showed a gradual decrease, in some cases a sharp decrease as shown in Fig. 11, with time after the exposure. Similar process was also observed on cholesterol content. It may be assumed, although small in number of animals examined, that the disturbance of phospholipid metabolism in the white matter caused by the exposure to carbon monoxide continues progressively after the exposure, while that in the gray matter recovers in early stage.

Fig. 11. Phospholipid content of brain tissues of rabbits.

Fig. 12. Cholesterol content of brain tissues of rabbits exposed to carbon monoxide for 6 hr.
As pointed out already in this report, three important problems have remained in clarifying the essential properties of carbon monoxide poisoning: (1) Are there any essential differences between acute carbon monoxide poisoning and chronic one in their poisoning mechanism?, (2) For the occurrence of carbon monoxide poisoning what factors except oxygen lack caused by the formation of carboxyhemoglobin concern with the nervous damage?, (3) The reason why the disorder of the central nervous system occurs especially on the white matter. In this study, the second subject was chiefly described.

When animals were exposed to various concentrations of carbon monoxide for a short period, in which carboxyhemoglobin formation proceeded linearly, the amount of lactate in the brain increased, and it seemed to be proportional to the amount of carboxyhemoglobin formed in the blood. According to further examination, the accumulation of lactate does not concern with the amount of carboxyhemoglobin and is depend on the velocity of carboxyhemoglobin formation. This examination was performed at an fairly extremed condition that the final content of carboxyhemoglobin of the blood was nearly 50%, and thus the animals would be in the state of oxygen lack. In spite of serious oxygen deficiency, the increase of lactate occured scarcely when carboxyhemoglobin formation proceeded slowly. It may be therefore considered that oxygen lack itself by carboxyhemoglobin formation causes no significant effect on energy metabolism in brain tissues, and moreover inner state changes of whole body caused by carboxyhemoglobin formation, if the velocity of the changes is too high to adapt, have some important effects on brain metabolism, although the effects may not be direct on the barin.

The findings that nervous disorder could not be explained in a satisfactory manner on the basis of hypoxia alone and that many other factors, which might be rather important, would concern with the occurence of carbon monoxide poisoning were further supported by the experiment carried out according to the technique of tubocurarine test. In this experiment, nearly irreversible damage of nervous system in carbon monoxide poisoning was observed semiquantitatively, while complete recovery took place in the case of the breathing of low oxygen air. The tubocurarine test may be the most convenient one for quantitative measurement of nervous disorder in living state.

In pararell with the functional disorder of the nervous system, the disturbance of phospholipid content in the white matter, which might develop to anatomical changes, was observed. This phenomenon will be further investigated in details. At any rate, from these findings, it was clarified that hypoxia caused by the formation of carboxyhemoglobin might not be the essential factor for the occurrence of carbon monoxide poisoning.

This suggestion might led us to the solution of the first problem about the difference between the acute and chronic carbon monoxide poisoning, because if
oxygen lack were not the essential factor, chronic carbon monoxide poisoning which
did not follow the formation of carboxyhemoglobin would be recognized to be
similar to acute carbon monoxide poisoning in respect to the neglect of carboxy-
hemoglobin. Exceptionally, when carboxyhemoglobin formation proceeded very
rapidly by exposure to a large concentration of carbon monoxide, the properties
of the poisoning would be necessary to be discriminated from the acute carbon
monoxide poisoning developed slowly and the chronic one. Though chronic carbon
monoxide poisoning has been generally considered to occur by exposure to a small
amount of carbon monoxide for a long period, the functional disorder of the nervous
system was observed in the animals exposed to 50 ppm carbon monoxide, which
is the value of MAC\textsuperscript{24} for about 6 hr. The nervous disorder caused by below 50
ppm of carbon monoxide showed nearly complete recovery. In this case, however,
if animals were further exposed continuously for a long period, the disorder might
be developed to the irreversible one.

Finally, an indicator for carbon monoxide poisoning, which is expressed by the
value of [carbon monoxide concentration]×[exposure time in hours]\textsuperscript{25}, will be dis-
cussed. This indication has been conveniently used to know the degree of in-
toxication in acute carbon monoxide poisoning, and thus it should be applied in
the cases of the duration of exposure below 6 hr. The correspondence between
indicator values and the symptoms has been considered as follows: no perceptible
effect at 300, sometimes effective at 600, headache and nausea at 900 and dangerous
to life beyond 1500. The value of 2000, which is, of course, dangerous to life, can
be obtained in several cases, for example, 500 ppm×4 hr, 1000 ppm×2 hr, 2000 ppm
×1 hr, 5000 ppm×24 min, etc. At these conditions of exposure were formed 40%
carboxyhemoglobin in the blood. As described already, the amount of lactate ac-
cumulation in the brain was nearly proportional to the concentration of carbon
monoxide or the velocity of carboxyhemoglobin formation. It is therefore clear
that the biochemical change in the brain at the condition of 5000 ppm×24 min is
far different from that at 500 ppm×4 hr. The indicator should be thus used care-
fully.

References

2) Brucher, J. M. (1967). *Carbon Monoxide Poisoning, Progress in Brain Research* (Edited by
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