CARBON MONOXIDE

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Carbon monoxide has ever fascinated biologists. To one group, concerned with fundamental processes, it represents an odd and simple gas which does not enter ordinarily into the normal economy of life, but which can intrude into and wreak havoc among a wide variety of respiratory mechanisms. To another group, responsible for health and efficient performance of men functioning in an industrial culture which employs fire in a multitude of forms, CO represents an everpresent hazard responsible, literally, for thousands of asphyxial deaths each year (128). These varied interests have stimulated thoughtful and precise analyses of the effect of CO on biological processes, ranging from enzyme systems in yeast to complex central neural functions in man. But a review of the world literature[1] of the last 60 years soon demonstrates that isolated studies of this nature float in a vast sea of reports composed largely of uncontrolled observation and unbridled speculation.

This unhappy state of affairs has simplified the compilation of this review. It is likely that certain important contributions may have been overlooked; some of the reports published on the European continent during the past decade have not been available for study. Other communications have been omitted deliberately: the experimental design, control observations or the technics, one or all, were open to some question. In other circumstances, where numerous reports were mutually confirmatory, only the original communication and a recent re-examination of the problem have been noted. The reviews of Killick (98), of Drinker (51A), and of von Oettingen (145) are recommended to the reader in search of a more extensive bibliography.

There has been, nevertheless, an orderly development in understanding of a number of phases of the CO problem. The recent World War II stimulated a number of valuable investigations, many of which were built on foundations laid during the years before. Much of this more recent work is so closely related to the earlier studies that it has appeared advisable not to limit the scope of this review to recent advances; consequently, a discussion of early communications has been undertaken wherever applicable.

There are certain aspects of the field which were not considered germane to this review. Exclusion of them should not be construed to indicate their unimportance. Many of the industrial facets of the problem are of prime importance; an introduction to the pertinent literature is available in the more extensive reviews by Drinker (51A) and by von Oettingen (145). Special problems arising in aviation have been reviewed earlier (111).

[1] Mrs. Mary Crawford Folk made this review possible by her meticulous collection of over 3000 references to CO.

The reviewer will be confronted repeatedly with the problem as to whether the reported effects of illuminating gas or engine exhaust fumes containing CO are equivalent to the effects of CO alone. There are clear indications that the effects cannot safely be equated (72). Industrial gases commonly contain several hydrocarbons which might be responsible for the actions attributed to CO or which might even protect from its effects (188). In any study, the use of pure CO in air or inert gas mixtures is essential to a final decision.

ANALYTICAL METHODS

The need continues for relatively simple, yet highly sensitive and accurate, methods for analyzing gas mixtures for very small but physiologically significant proportions of CO. The principles of the classical analytical methods have been described clearly by Sendroy in Drinker's monograph (51A). In recent years, certain new approaches have been developed. There is none which is economical and simple with respect to both time and equipment. Roughton and Root (173) have improved the method of Sendroy and Fitzsimmons (191), an adaptation of Nicloux's principle, which takes advantage of the affinity of reduced hemoglobin (Hb) for CO. In this method, Hb in whole blood is employed to scavenge CO from the gas sample. With the improvements noted, the gas sample must be large (400 to 500 ml.), but analyses accurate to within about 1 p.c. may be made on gas mixtures containing 0.005 to 0.03 p.c. CO. Although accurate and sensitive, the method is both time-consuming and finicking and cannot be applied easily to a large number of analyses. During the recent decade, the Gas Chemistry Section of the National Bureau of Standards, under the leadership of Shepherd, has developed a rapid method for determining small amounts of CO in gases (194). The method is based on the color changes produced by CO passing through a silica gel, impregnated with palladium sulfate and ammonium molybdate. The sensitivity of the method is extraordinary: the gel will detect 1 part of CO in 500,000,000 parts of air; it is capable of differentiating to 0.0002 p.c. The preparation of the indicating tubes and of the necessary CO standard gas mixtures cannot be undertaken lightly by the ordinary laboratory, but if a supply of tubes and mixtures can be obtained, then the analyses themselves are the essence of simplicity. Comparative analyses between this and conventional methods have established its high order of usefulness (194A). Other developments in analysis have made use of refinements in calorimetry (92) and in infra-red absorption spectrophotometry (56).

With increasing attention to the effects of small amounts of CO on the behavior of Hb and on performance in man, the requirements for extremely precise analyses of COHb content of blood became critical. The method of Sendroy and Liu (193) had provided earlier the best method based on the Van Slyke-Neill apparatus. Horvath and Roughton described several alternate modifications which are useful (86), and Van Slyke and his collaborators have added important technical refinements (219). The Roughton-Scholander microgasometric syringe technic, applied to the analysis of CO in blood, provided a simple and rapid method using very small amounts of blood (40–120 c.mm.) and furnishing an accuracy of from 0.03 to 0.05 vol. p.c. (183). Finally, Roughton and Root com-

bined the Van Slyke-Neill and Roughton-Scholander technics in a method requiring 0.5 ml. of blood and providing an accuracy of 0.02 vol. p.c. (172). This is an elegant method which has refined appreciably the capacity for precise measurements of CO in blood.

Spectrophotometric methods have been extended both in principle and in design of more precise apparatus (50, 84, 85, 100). Use of spectrophotometry for measuring CO in flowing blood has been described (129). Andrews and Horecker (6) have designed an extremely useful and simple spectrophotometer which makes use of spectral absorption in the near infra-red; the order of accuracy is somewhat less than the most precise gasometric methods.

There need never be an apology for a moderate preoccupation with methodology; and, in the case of CO, attention paid to precision of analysis is essential. In retrospect, it now appears likely that unrecognized errors inherent in the analytical methods used by Haldane and his colleagues were indirectly responsible for the once polemic but now abandoned concept of active secretion of oxygen across the alveolar membrane.

Effects of CO not mediated by its action on hemoglobin

It has been said many times that the effect of CO on man may be attributed to two actions and, in essence, to these two actions alone: *a*) occupation of the Hb molecule by CO, with a resultant decrease in the O_2 transport capacity of the blood; and *b*) alteration of O_2Hb dissociation characteristics produced by COHb, with a resultant impaired unloading of O_2 at the tissues. This has been a helpful clarification of principle, and, in the light of much recent work, probably still holds true in the main. Too literal an acceptance of these statements, however, may divert attention from the fact that CO does, under certain circumstances, produce profound effects on mechanisms other than the oxygen-hemoglobin system (49). Although these effects may appear superficially to have no bearing on the problem of CO intoxication in man, nevertheless, the possibility remains that some of these effects may underlie certain disturbances in function induced by exposure to CO. Also, some knowledge of the complete spectrum of biological actions of CO should furnish a better basis from which to analyze the effects of CO on man.

In early studies it was discovered that small mammals could survive exposure to an atmosphere of CO sufficient to convert all Hb to COHb if the partial pressure (p) of O_2 was enough to dissolve O_2 in physical solution in amounts adequate to meet minimal metabolic needs (74). The reasonable conclusion was drawn that no consequential interference with cellular processes had occurred. However, as early as 1888 Frankland had noted that the growth of several species of bacteria was inhibited in an atmosphere containing CO (65). More recent investigations of effects of CO on bacterial metabolism have furnished some striking examples of intense interference with normal mechanisms. *Azotobacter*, respiring in an atmosphere containing 0.2 p.c. CO, is inhibited with respect to its capacity to fix nitrogen (119). A specific hydrogenase operating in the intact bacterial cell is likewise inhibited (231). In certain luminous bacteria,

overall respiration is depressed by CO; if the environmental CO/O_2 ratio is low, light emission is enhanced; with increasing proportions of CO the degree of light emission falls (184).

There are several isolated botanical observations which exemplify the effect of CO on other systems not dependent on hemoglobin. Lind and Wilson found that as little as 0.01 p.c. CO in the atmosphere depressed N_2 fixation by red clover, and 0.05 p.c. blocked fixation completely (118). This was a reversible inhibition. Catalase, found in rich concentration in the avocado seed, is inhibited specifically by CO but not by CN (127). Furthermore, J. B. S. Haldane noted that cress seed failed to germinate in the presence of CO (77).

There have been a number of observations on the effect of CO on respiration of bakers' yeast. With this form the detectable effects are seen first only when the pCO is extremely high in comparison to the pCO which produces effects in mammals. Warburg in his early studies demonstrated clearly that the inhibition of respiration was a function of the ratio pCO/pO_2 in the atmosphere, an observation which he interpreted to indicate competition between CO and O_2 for his Atmungsferment (223, 224). There remained a portion of respiratory activity which was not susceptible to inhibition by CO. Keilin showed that CO inhibited indophenol oxidase in yeast (94). Stannard found that CO might stimulate, depress or not affect respiration of yeast (204); and Winzler found an inhibition due to CO which was not a function of the environmental pO_2 (232).

Scattered observations on the depression of respiration by CO have been made in a number of forms: paramecia (39), sea-urchin eggs and embryos (120, 121), grasshopper embryos (15), fruit fly pupae (233) and adult wax moths (77). In fact, the action of CO on respiration is not uniformly depressant; the unfertilized sea-urchin egg and the grasshopper embryo, in the inactive stage of diapause, both respond to CO by a rise in respiration.

The basis for assuming that these various observations on non-mammalian forms have little relevance to an understanding of the mechanism of CO intoxication in man is mainly that the pCO required to affect respiration in lower forms is so great. However, it may be pointed out that measurement of overall respiration is a relatively crude index. If the same index were employed to estimate the effects on man of low pCO in inspired air the results would be similarly negative and misleading. The O_2 consumption of man with 30 p.c. of his circulating Hb converted to COHb is not altered (8), but a variety of finer, specific functions exhibit a gross deficit.

The problem resolves itself into the need for assessing the effect of CO on highly specialized functions. Examples of such demonstrations are furnished by measurements of N_2 fixation in *Azotobacter* and red clover, and by observations that high pCO is toxic for rats even when adequate supplies of O_2 are provided in physical solution in plasma (77).

In view of these considerations, and the affinity of so many tetrapyrrol respiratory pigments (hemes, oxidases, catalases) for CO, it would seem proper to quality the usual statement regarding the reasons for the toxicity of CO for man. It is entirely possible that certain selective effects of CO may be owing in

part to damage to specific systems by means other than the anoxemia produced by formation of COHb, and the site of common action might well be the wide spectrum of tetrapyrrole respiratory pigments.

Metabolism of CO

It is a curious but common attitude among biologists to view with considerable distaste the introduction of concepts requiring the admission of new chemical elements and compounds into the existing scheme of metabolic economy. The literature abounds with sorry examples of attempts at such introductions based on faulty technics, and these experiences account, perhaps, for the wariness encountered by the investigator who reports the participation of new substances in the established order. In point of fact, this scepticism is healthy; nevertheless, the past years have seen, for example, rigorous proof of the importance of Zn in carbonic anhydrase, of the presence of Co in extrinsic hemopoietic factor, and of the possession by the rabbit of enzymes which hydrolyze a botanical alkaloid (atropinase) and a synthetic fluorine derivative (fluorophosphatase). In view of these developments it appears necessary to accept the possibility that several substances, now thought to be inert, may play a normal or unusual role in several intracellular processes.

Another example of such a development begins with the report by Fenn and Cobb in 1932 that the total gas consumption of frog muscle rose 1.5 to 3 times when respiring in an atmosphere which contained 79 p.c. CO and 21 p.c. O_2 (57). This effect was still detectable but much diminished in a muscle mash. In muscle which had lost irritability, either spontaneously or by treatment with KCl, the stimulatory effect of CO was decreased. Block of lactic acid production by bromacetate did not abolish the CO effect. Illumination of the muscle had no effect on the action of CO, in contrast to the effect of light on CO toxicity and Hb affinity. The observed fall in apparent respiratory quotient as measured in the Fenn volumeter suggested that frog muscle oxidized $CO \rightarrow CO_2$. It should be noted that the oxidation of CO to CO_2 has an intrinsic RQ of 2 and that in fact the RQ rises; but the Fenn volumeter which does not distinguish between the disappearance of CO and O_2 makes the apparent RQ of $CO \rightarrow CO_2 = 0.66$. In a companion paper, the effect of CO on a variety of tissues was reported (58). It appeared that respiratory stimulation by CO was limited virtually to striated and cardiac muscle. Rat muscle was significantly less responsive than that of frog. Gasometric determinations of the O_2 consumption satisfied the investigators that muscle did indeed oxidize $CO \rightarrow CO_2$. By analogy with Negelein's observation that hemin effected oxidation of $CO \rightarrow CO_2$ in the presence of low pO_2, it was suggested that Warburg's iron-containing respiratory ferment played a role in this phenomenon.

The findings were questioned because the determination was essentially indirect and for reason of possible technical errors. However, in 1934 Schmitt and Scott confirmed the general finding (182). By somewhat different technics they recorded stimulation of respiration by 80 p.c. CO in striated muscle, stomach, liver, spleen and especially myocardium. No such effect was noted in skin, nerve,

kidney or intestine. When the O_2 percentage of the atmosphere was reduced from 20 to 10, only liver, muscle and myocardium continued to display increased respiration. From a technical point of view the data reported furnish satisfactory support of the Fenn-Cobb phenomenon but are not completely satisfactory for establishing the different reactions of the various tissues studied.

In the intervening years the validity of the original deductions has been established firmly by an orderly series of studies at the University of Rochester. Hursh studied the respiratory and heat production patterns of frog muscle stimulated and recovering in 79 p.c. CO (89). Recovery proceeded at the same rate in CO as in air, but the excess of O_2 consumption and the recovery heat production were diminished. No evidence could be found to indicate that CO inhibited formation of lactic acid; and the effect of CO persisted after treatment with iodoacetate. These results appeared to point to an enhancement by CO of the efficiency of recovery processes. Carleton and Fenn found that the excess metabolism of frog muscle induced by CO was not modified when the overall metabolism was accelerated by increasing the concentration of potassium in the environment, or by varying the pH from 1 to 10; if pH was reduced below 1 or increased over 10, the CO effect vanished (34). Several marine forms failed to exhibit the respiratory response to CO. In 1939 Stannard showed that the criticisms based on questions of technic were invalid and reconfirmed the original observations (203, 205). His work showed further that the excess O_2 consumption induced by CO was not a ceiling effect: a number of agents which increased resting respiration to high levels did not affect the action of CO. Some agents, like caffeine, however, raised respiratory activity to a level at which the CO effect could not be demonstrated. In some observations it was demonstrated that the CO effect could be evoked even when the cytochrome-cytochrome oxidase system had been inhibited, as it is by CO (211). Stannard's interpretation of these results proposed that in frog muscle CO was oxidized by enzymes similar to, but differentiated from, those systems carrying on respiration during rest and activity. The action of CO was twofold: it inhibited the Warburg-Keilin system yet stimulated conversion of $CO \rightarrow CO_2$. The suggestion was made that a process coupled to catalase activity might provide the pathway for conversion, and a similar mechanism has been suggested recently by Chance (35). More recently Stannard has suggested that CO conversion might be related to myoglobin; the rationale of this suggestion is based on the coincidence of active CO conversion and high myoglobin concentrations in striated and cardiac muscle, while liver, which contains much catalase and xanthine oxidase, has little converting capacity (206). Lindahl has reported studies of the frog sartorius exposed to CO and has found that the Fenn-Cobb effect is not completely reversible; he reported that after an hour's exposure to CO the RQ of the muscle rises from 0.7 to 1.0 and that this is not the result of formation of lactic acid (122, 123). He concluded that part of the rise in respiration is not owing to $CO \rightarrow CO_2$.

Recently the Rochester group has made a series of observations on the metabolism of CO in isolated tissues and in the intact animal (turtles, mice) by means

of modern, refined analytical technics and by means of isotope tracer technics employing C^{14} (40, 41, 43). In a variety of experiments it was established again that frog muscle converts $CO \rightarrow CO_2$ by a mechanism which was susceptible to inhibition by azide and by hydroxylamine. But of equal interest was the clear demonstration that in prolonged experiments both turtles and mice oxidized $CO \rightarrow CO_2$. Mice were found to oxidize approximately 0.24 c.mm./g. body wt./hr. when exposed for 4 days to an atmosphere containing 0.07 to 0.09 p.c. CO. If this figure were applied, without reference to metabolic rate, to a 70 kg. man the comparable rate of oxidation of CO would approximate 20 ml./hr., an amount which would constitute less than 10 p.c. of the CO respired. For reasons such as this the conversion phenomenon, even if it exists at this level of activity in man, probably plays a scarcely significant role in determining the rate of formation of COHb, the rate of elimination of CO, and the equilibrium reached or in the development of acclimatization.

Experiments on man with the short-lived isotope, C^{11}, showed that in 60 minutes less than 0.1 p.c. of absorbed CO was converted to CO_2 (216). In other studies, which were designed to produce rapidly a carboxyhemoglobinemia of 5 to 20 p.c., the rate of elimination of CO was measured gasometrically for 4 hours (171). In 3 such experiments the recovery of CO averaged 95.6 p.c., and in view of the possibility of slight leaks in the experimental system it was concluded that these data made it highly unlikely that metabolism of CO had occurred. Clark and his colleagues have pointed out that their observations on conversion in intact animals were long in duration and that if the conversion process were slow to start the shorter experiments might obscure a demonstration of the conversion (40, 41). On the other hand the possibility remains that the 4 p.c. of CO which was not recovered was indeed converted.

There are two odd sets of data available which may be interpreted to establish the endogenous formation of CO in man. Sjöstrand reports excretion rates varying from 0.5 to 1.05 ml./hr. and concentrations of CO in alveolar air of approximately 0.002 p.c. both before and after 5 hours of respiration through a filter which prevented inhalation of ambient CO (199A). Nicloux and others of the French school have presented data which suggest formation of CO (142).

At the present time it would appear judicious to bear in mind that CO produces effects which are separate from that produced on Hb: both inhibitory and stimulatory actions on a variety of respiratory enzymes have been proved; the conversion of $CO \rightarrow CO_2$ is established firmly; the endogenous formation of CO may occur, although these observations require further confirmation. The role played by these actions of CO is probably scarcely detectable in man in relation to the overwhelming effect on Hb, but these actions must be taken into account whenever precise equilibrium or balance studies are to be interpreted. Knowledge of the basis of these properties of CO may in time lead to a clearer understanding of the mode of function of a number of intracellular respiratory mechanisms.

CARBON MONOXIDE, OXYGEN, AND HEMOGLOBIN

Before reviewing certain phases of the literature dealing with the interactions of CO, O_2 and Hb, it would appear proper to draw attention to the wealth of

information which has accumulated with respect to the properties of hemoglobin (106, 169). The extraordinarily variable O_2- and CO-binding properties of Hb derived from diverse animal forms, ranging from marine worms to mammals, make it necessary to define rigidly the source of Hb studied (63). This variability occurs likewise within the mammalian class so that, unless stated specifically to the contrary, the term Hb may be assumed to apply to human blood. There is, in addition, evidence to indicate that the blood of normal men may contain appreciable amounts of Hb which does not take up CO (5).

Douglas and the Haldanes first derived certain "laws" which described equilibrium conditions obtaining when Hb was exposed to a gas mixture containing CO and O_2 (48, 76). The essential validity of these descriptions has never been in question, but their application to special cases has been extended broadly in the years since the original deductions were made. The first "law" stated: *"When a solution containing haemoglobin is saturated with a gas mixture containing O_2 and CO the relative proportions of the haemoglobin which enter into combination with the two gases are proportional to the relative partial pressures of the two gases, allowing for the fact that the affinity of CO for haemoglobin is about 300 times greater than that of O_2."* These relations may be described simply by the following expression:

$$\frac{[COHb]}{[O_2Hb]} = \frac{M pCO}{pO_2}$$

where the concentrations of the hemoglobin compounds are related to the partial pressures of the gases, and M is the relative affinity constant. It should be noted that this expression describes the relationship which held for the special case where no reduced Hb was present in the system.

The relative affinity constant, M, has been determined by several groups of investigators. Douglas and the Haldanes found M to range from 220 to 290 (48). Killick determined M to range from 233 to 272 (96, 99). Sendroy, Liu and Van Slyke found M to average 210 $\pm$ 2.5 p.c. (192). These various determinations were carried out on shed blood equilibrated in tonometers, and there remained a question as to whether changes may have occurred during equilibration of the blood with the gas mixture. Lilienthal and Riley determined the relative affinity coefficient in 3 subjects who were in equilibrium at high altitude with respiratory gas mixtures containing from 0.005 to 0.015 p.c. CO (116). Under these circumstances M was 204 $\pm$ 10 p.c.; this value corresponds fairly satisfactorily with that found by Sendroy and provides evidence that the equilibrium attained *in vivo* is the same as that which results in the tonometer. Furthermore, there was no evidence to suggest that the value of M varies during exposure to lowered pO_2. On the other hand, it must be emphasized that although the value of M may well be a constant in the blood of man, yet its value varies enormously from species to species (63), and that a similar variation is noted among several respiratory pigments in the individual animal (137).

Roughton and Darling showed that the expression presented above holds for *in vitro* systems containing appreciable proportions of reduced Hb (168), and a similar validation has been made for *in vivo* relations even though there are

present only small amounts of COHb and moderate quantities of reduced Hb (116).

The second Douglas-Haldane "law" stated, *"Where the pressure of O_2 and CO together is insufficient to saturate the haemoglobin, the dissociation curve, so far as reduced haemoglobin is concerned, will be the same as when oxyhaemoglobin alone, or CO-haemoglobin alone, is present at a pressure equivalent in saturating power to that of the O_2 and CO together; and the O_2 and CO will divide their combined share of haemoglobin in just the same proportions as if they together combined with the whole of the available haemoglobin."* This "law" may be rephrased in these terms: in blood exposed to O_2 at a partial pressure pO_2 and to CO at a partial pressure pCO, the total hemoglobin saturation,

$$100 \times \frac{[COHb] + [O_2Hb]}{[COHb] + [O_2Hb] + [\text{Reduced Hb}]},$$

is the same as it would be in the absence of CO, if pO_2 then equaled $pO_2 + M\text{pCO}$. Thus, by means of Roughton and Darling's treatment (168), it becomes possible to view the combination of CO and O_2 with Hb as though they were the same gas, allowing for their disparate affinities. These relations imply likewise that the following pairs of functions may be described by the *same* standard oxyhemoglobin dissociation curve (116):

(A) pO_2 and $100 \times \frac{[O_2Hb]}{[O_2Hb] + [\text{Red. Hb}]}$ in the absence of CO,

(B) $M\text{pCO}$ and $100 \times \frac{[COHb]}{[COHb] + (\text{Red. Hb})}$ in the absence of O_2, and

(C) $pO_2 + M\text{pCO}$ and $100 \times \frac{[O_2Hb] + [COHb]}{[O_2Hb] + [COHb] + [\text{Red. Hb}]}$.

The validity of using the same dissociation curve to describe the behavior of these complex mixtures of CO, O_2, COHb, O_2Hb and Red. Hb was established by Roughton and Darling by means of equilibria attained *in vitro* (168); the same equivalence has been shown to hold *in vivo* as well (116).

The third "law" states in part, *"Oxygen is given off from oxyhaemoglobin . . . in a totally abnormal manner when the blood is highly saturated with carbon monoxide . . . the dissociation of the oxygen is altered in such a way that the oxygen comes off less readily, or at a lower pressure than in normal blood. . ."* This reversible phenomenon, often called the "Haldane effect," results from the action of COHb on the dissociation characteristics of the remaining O_2Hb. In fact, Haldane's theoretical treatment was based on the effect of O_2Hb on the COHb dissociation curve (76). Stadie and Martin reported a converse study over a limited range of the effect of COHb on the O_2Hb dissociation curve (202). Finally, Roughton and Darling studied the effect of COHb on O_2Hb dissociation over a wide range of equilibria attained *in vitro* (168). The study of the "Haldane effect" *in vivo* in men who had come into equilibrium with ambient air containing low concentrations of CO confirmed these findings (116).

From these relations Roughton and Darling, as well as Pappenheimer (150) in an independent essay, reviewed the basis for the profound physiological effects produced when relatively small amounts of Hb have been bound by CO (150, 168). The essence of this treatment is the plotting of the total amount of O_2Hb, or O_2 available, against the pO_2 for varying concentrations of COHb in the mixture. When the data are presented in this fashion it becomes clear at once that in concentrations less than 40 p.c., COHb produces relatively easily compensated restriction in the amount of O_2 available for delivery at the tissues; above concentrations of 40 p.c. COHb produces a critical restriction in the amount of O_2 available. An experimental application of these relations has been made by Lester and Greenberg (108). This form of analysis also provides an explanation of Haldane and Smith's startling observation that mice, surviving at very low oxygen tensions, were benefited by the addition of small amounts of CO to the respiratory mixture; since this interesting phenomenon occurs at O_2 tensions so low as to be incompatible with life in man it will not be discussed further.

The relationships of CO, O_2 and Hb which have been discussed above are those existing when equilibrium has been reached. Apart from their fundamental importance, there are a number of circumstances wherein the kinetics of reactions involving CO, O_2 and Hb require definition. One such example occurs in studies of the rate of uptake and elimination of CO by blood passing through the pulmonary capillaries; without approximate definition of the combination and dissociation velocities it is not possible to assess properly the limiting roles played by rate of circulation, volume of blood exposed to alveolar air, duration of exposure, etc.

It will be appreciated that the measurement of the kinetics of this system is made extremely difficult technically by the rapidity of the reactions and the analytical problems to be solved. However, over the past 25 years, beginning with the early paper of Hartridge and Roughton (79), there has issued from the laboratories at Cambridge University an extraordinary series of studies pursued by Roughton and his colleagues (13, 137, 164, 165). As an example of sustained interest which has stimulated the development of technics increasing in precision and elegance, this is a series of papers which is of especial importance. The general principles were worked out earlier with sheep hemoglobin in solution, and then later with erythrocyte suspensions. Finally, the approximate kinetics was analyzed by Roughton using human erythrocytes and a reaction temperature of 37°–38°C. (166). In general the kinetic data in human blood were in accord with the expression derived from solutions of sheep Hb. In whole blood, additional factors which might alter the rates observed in solutions of Hb are the necessity for gas *a*) to diffuse through the red cell membrane, and *b*) to diffuse through the red cell water. Roughton calculates that the minimum value for the diffusion constant of the red cell membrane is such that for each mm. of Hg pressure gradient of pO_2 21.5 p.c. increase in O_2Hb occurs each second. For the same conditions the corresponding figure for CO is 18. Comparison of calculated rates of the reaction $CO + O_2Hb \rightleftharpoons O_2 + COHb$ in solution and in red cells for human blood at 37°C. yielded some interesting information on kinetic relations.

At high oxygen tensions, pO_2 = 400 mm. Hg, the rate of formation of COHb was about the same whether in solution of Hb or in red cell suspensions; when pO_2 was 106 mm. Hg, the approximate tension in alveolar air, the rate of reaction in red cells was about 20 p.c. slower than the reaction in solution of Hb. The half-time for dissociation of COHb in the body was calculated to be of the order of 7 seconds. A more recent summary, which should be consulted for a resumé and complete bibliography, indicates that the half-time for dissociation of COHb (sheep cells) may be of considerably longer duration (170).

From the wealth of data which have been only sketched above, and the figures derived from them, Roughton was able to combine experimental observations in man to calculate the time spent by blood in the human lung capillary (167). The importance of this approximation rests in the need for knowing how long a period is available for gaseous exchange for any unit volume of circulating blood. The duration of exposure of capillary blood to alveolar air was 0.75 ± 0.25 sec. at rest and during heavy work the increase in circulatory rate reduced this period to 0.34 ± 0.1 sec. The data provided also the means for estimating the instantaneous total volume of blood exposed to alveolar air: at rest it averaged 60 ml. and during work rose only to 95 ml. If these calculations are proved to describe accurately the expansion of circulation through alveolar capillaries, then the concept that exercise widens the diffusing capillary bed significantly will require revision. Other deductions applicable to the uptake and elimination of CO will be treated below.

Uptake and elimination of CO in man

Haldane, in a series of extraordinarily punishing experiments on himself, made the first study of the rate of uptake of CO from inspired gas mixtures (75). Since then a number of similar studies have been reported. With the exception of the three war-time investigations, to be discussed in some detail, the other studies gave somewhat irregular results. The discrepancies would appear to result from the fact that certain factors, known now to affect rate of uptake of CO, were not controlled or measured. Likewise, the methods for analysis of COHb were perhaps not as reliable as might be desired, especially in the lower range of COHb concentrations. For these reasons no discussion of the prior studies will be undertaken; the interested reader may find complete references to these works in the papers discussed below.

On theoretical grounds the rate of uptake and elimination of CO might be determined by the following factors: *a*, pCO of inspired air; *b*, pO_2 of inspired air; *c*, total ambient pressure; *d*, pCO and p.c. COHb existing at zero time, as well as nearness to equilibrium saturation; *e*, duration of exposure; *f*, alveolar ventilation, which includes the factors introduced by total ventilation, distribution, dead space and the diffusion constant of the lung; *g*, circulation through lung, which includes rate and volume of pulmonary flow, duration of exposure of blood to alveolar air, and instantaneous amount of blood in alveolar bed; *h*, hemoglobin, and perhaps myoglobin, mass; and *i*, the kinetics of the combinations and dissociations between CO, O_2 and Hb.

The three papers to be reviewed in some detail furnish data from which some assessment may be made of the relative importance of the various factors listed above (62, 113, 148). Each group was able to formulate an expression which predicted with considerable precision the rate of uptake of CO during the earlier stages of exposure. The expressions vary, but each takes into account the following factors in common: pCO, duration of exposure and the ventilation rate. It may be concluded, therefore, that these three factors determine the rate of uptake of CO in normal man, and that the other factors are constants or alter reciprocally and thus cancel any detectable effect. This conclusion is limited necessarily to normal man. Other exceptions, such as unusual O_2 tensions in inspired air, will be considered below.

Forbes, Sargent and Roughton (62) examined the effects of varying pCO, pO_2, barometric pressures, time of exposure, degree of activity and also the related functions of ventilation and circulatory rate, and inter-individual variations. Their data indicated that

$$\text{the rate of CO uptake} = K\text{pCO} \times \frac{\text{p.c. COHb at equilibrium} - \text{p.c. COHb at time } t}{\text{p.c. COHb at equilibrium} - \text{p.c. COHb at time zero}},$$

where K = a constant which varies with activity of the subject. A simplification of the formula gives the p.c. saturation of COHb in the blood when there are known the p.c. of CO in the inspired air, the degree of activity gaged roughly by ventilatory and pulse rates, and the time of exposure.

Pace, Consolazio, White and Behnke (148) formulated the following expression from their data:

$$\text{p.c. COHb} = \frac{\text{p.p.m. CO} \times \text{minute vol.} \times \text{exposure time}}{4650 \times \text{blood vol.}}.$$

Lilienthal and Pine (113) found that the increase in p.c. COHb was predicted accurately by the simple formula:

$$\text{p.c. COHb} = (\text{pCO inspired} \times \text{time (min.)} \times \text{ventilation/min.}) \times 0.05.$$

The virtual identity of the three expressions which were developed independently may be demonstrated by calculating the predicted increase in p.c. COHb by each method for a variety of conditions. When this is done the variation among the three different expressions is usually of the order of 1 p.c. COHb or less. Pace has developed nomographs for ready prediction of uptake of CO (146, 147).

It is apparent that these expressions describe a constant rate of CO uptake. However, since the pCO of the blood will come into equilibrium with the alveolar pCO within a finite period, it will be seen readily that the curve describing the uptake of CO to equilibrium must be asymptotic. The probable explanation of the linear uptake in the first period of exposure rests with the fact that the pressure gradient of CO between the alveolar air and the mixed venous blood

entering the pulmonary capillaries remains virtually constant until sufficient CO has been absorbed and distributed throughout circulating hemoglobin, and perhaps fixed myoglobin, to create a significant back pressure of CO in the blood. Then, as the back pressure rises, the pressure gradient across the alveolar membrane falls, the rate of CO absorption slows and the proportion of CO absorbed from the inspired mixture decreases steadily from its initial value of about 50 p.c. When equilibrium is reached the net transfer of CO and the rate of increase in COHb will have become zero. Inspection of the uptake curves suggest that the initial linearity of rate is maintained for all practical purposes until approximately one-third of the final equilibrium concentration of COHb has been reached (154). During the following periods there are changes in pCO of alveolar air and of blood which are difficult to predict on a theoretical basis. A more precise experimental definition of the changing rates of CO absorption after the initial period of linear uptake is needed to fill the gaps in our present knowledge.

All three groups found that reduction in barometric pressure had no detectable effect on the rate of uptake of CO. Tolerable reduction in pO_2 of the inspired gas mixture by exposure to simulated moderate altitudes also produced no effect. When air in the inspired mixture was replaced by O_2, appreciable reductions in rate of uptake of CO were observed (62, 113), as would be anticipated from Roughton's finding that the rate of chemical reaction of CO with Hb varies inversely with pO_2 (165). Forbes and his colleagues discovered individuals in a group of 7 who varied as much as ± 20 p.c. from the predicted rate of CO uptake; they attributed these anomalous findings to individual variations in the ratios of tidal air to dead space and in the diffusion constants of the lung. Pace *et al.* examined 32 subjects and Lilienthal and Pine studied 9; no similar degree of variation was discovered.

There is little available information on the rate of elimination of CO (202). The general trend of scattered reported observations indicates, as might be anticipated, that elimination of CO is more rapid with higher concentrations of COHb (high pressure gradient of CO between blood and alveolar air) and then slows as the concentration falls. Roughton and Root report that in normal men breathing air, half the CO is eliminated in 240 minutes at a logarithmic rate, and that by breathing O_2 the elimination half-time is reduced to 40 minutes, a six-fold acceleration (171). By contrast Lilienthal and Pine found that their subjects would fall from 20 p.c. to 10 p.c. COHb in 90 minutes while breathing air; by breathing O_2 the elimination half-time was reduced to 15 minutes, again a six-fold acceleration (114). Pace, Strajman and Walker studied elimination rates in 14 subjects, aged 20 to 65 years (149). The elimination half-time varied from 34 to 82 minutes; the correlation with age was direct and of high order, for it appeared that each year of life increased the half-time by 1 p.c., perhaps reflecting the aging process in cardiorespiratory functions. Some of the complicated factors which affect elimination have been studied and discussed by Roughton and Root (171). Other factors which bear on methods of treatment of CO intoxication will be reviewed below.

GENERAL SYMPTOMATOLOGY

There have been many studies which have correlated the amount of COHb in blood with the development of subjective symptoms (51A, 98, 145, 176). As precise knowledge as possible is of great importance to industrial hygienists. No new facts have been uncovered in late years, but certain comments on the studies, referred to in the reviews indicated above, may be appropriate.

The symptoms of mild CO intoxication are not distinctive: moderate frontal headache, lassitude and drowsiness, faintness, occasionally nausea. In fact, many of these symptoms will be experienced by persons required to perform monotonous, stereotyped jobs when no exposure to CO exists. When blood concentrations of COHb rise to about one-quarter saturation and above, the symptoms become more severe and stereotyped and include breathlessness on exertion. Under these circumstances, no doubt exists but that the more severe symptoms may be attributed rightly to CO intoxication. The degree of somatic consciousness of the experimental subject plays a large role in determining the intensity of symptoms at low levels of blood COHb. For example, Haldane noted virtually nothing remarkable when his blood was one-third saturated with CO; other workers have observed headache at saturations of 7 to 15 p.c. and in one subject who exercised when his blood COHb was 7 p.c. an alarming train of symptoms ensued (176). Since the blood of any heavy smoker contains 7 p.c. of COHb and more, the gravity of concentrations of this order is questionable. Emphasis must be laid on the fact that these comments apply to subjective symptoms only; small concentration of COHb of this order do indeed produce measurable impairment of certain delicate and complex functions to be discussed below. Furthermore, prolonged mild carboxyhemoglobinemia produces effects when short exposures do not (116).

The literature is filled with reports and studies of what purport to be chronic CO poisonings. There is little doubt that certain special occupations expose workers to CO. There is great doubt that the protean symptomatology attributed to such exposures bears any relation to CO; if it does, it remains unproved. An excellent example of a study which puts this problem in what appears to be a proper perspective was carried out in the Holland tunnel (197).

TOLERANCE AND ACCLIMATIZATION

Tolerance to various stresses and the increase in tolerance accompanying acclimatization and adaptation have been the subject of much physiological and pharmacological study. One phase of the attack has been an assessment of tolerance and acclimatization to the hypoxia induced by high altitude. On this subject a wealth of observations has been reported (87, 218). Some of them are directly applicable to the effects of CO, but there are clear indications that in the case of CO there are special and peculiar aspects which require differentiation from the general effects of hypoxia.

The first problem arises in any attempt to furnish a definition of "tolerance" and "acclimatization." In some cases simple survival under a given stress may

be taken to define tolerance or acclimatization; in others, preservation of a special function at full efficiency may be the criterion. The problem becomes more complex when it is realized that under increasing loads of stress a variety of functions begin to deteriorate serially. An example of this is seen in a study of functional impairment induced by low oxygen tensions: scotopic vision may show measurable decrement at very slight increase in pressure-altitudes while auditory function is maintained at levels of hypoxemia bordering on collapse. With these reservations it is possible to assess the tolerance and acclimatization which man and experimental animals display.

The most delicate indication of the effect of very small increments in COHb was described by McFarland and his collaborators (126). Visual brightness discrimination was impaired significantly when an increase of 4 p.c. COHb saturation had occurred. In one instance there was detectable impairment when, after the subject had smoked one cigarette, his COHb saturation rose 2 p.c. Lilienthal and Fugitt studied the summed effects of small increments of COHb and of mild hypoxemia by measuring critical flicker fusion frequency, a function also dependent on the entire visual apparatus (112). At altitudes of 5000 and 6000 feet, the added stress of 5 to 10 p.c. COHb resulted in appreciable but reversible deterioration in this special function. By contrast there are other studies which indicate that other somewhat similar functions were not impaired by even larger increments in blood saturation of COHb. Vollmer, King, Birren and Fisher measured visual fields, body sway and flicker fusion frequency at 10,000 and 15,500 feet with and without the additional stress of 5 to 22 p.c. COHb (220). The impairment detected at increased pressure-altitude was the same whether or not COHb was added. Abramson and Heyman could detect no consistent impairment of dark adaptation in subjects whose COHb saturation reached 30 p.c. (1). This finding is difficult to reconcile with the deterioration in night vision which has been demonstrated to begin at pressure-altitudes of 5000 feet. Finally, in the realm of motor performance a battery of visual, psychomotor, coordination and reaction time tests revealed little or no impairment when one third or more of the circulating Hb had been converted to COHb (47, 61).

Pitts and Pace employed the pattern of pulse rate response to exercise as a measure of the effect of low concentrations of COHb (155). From a series of observations they concluded that a distinct alteration in pattern was produced by 13 p.c. COHb or by exposure to a pressure-altitude of 7000 feet. They calculated that the increment in pulse rate response for each 1 p.c. rise in blood COHb was equivalent to that obtained by a rise of 335 feet in pressure-altitude. The observations of Asmussen and Chiodi showed that, although heavy work can be carried on with a blood COHb of 30 p.c., nevertheless the circulatory response is much more brisk (8). As with hypoxia, crude tolerance to CO measured by survival in the usual experimental animals is greater in the neonatal period, and greater in females than males (27, 200, 227).

In summary, it may be said that certain refined functions exhibit impairment when relatively small amounts of circulating Hb have been converted to COHb and the arterial pO_2 may be presumed to be at its normal level. The

effects of summed CO and hypoxia were predicted on a theoretical basis by Heim (81). As the degree of carboxyhemoglobinemia increases, functional alterations become overt serially in an increasing number of systems, certain of which will be reviewed in more detail below.

With regard to the phenomenon of acclimatisation the picture becomes somewhat murky. There is unequivocal evidence that, as with hypoxia, repeated exposures to CO evoked responses which tend to reduce the effects of hypoxemia in general. The early study of Nasmith and Graham in 1906 showed that prolonged exposure of guinea pigs to CO stimulated a compensatory polycythemia which balanced in degree the amount of Hb bound by CO (140). They emphasised for the first time the similarity of this response to that seen in acclimatisation at altitude. In the light of present-day knowledge of bodily reactions to stress, it is of considerable interest to find that in the group of animals stressed severely by CO the number of eosinophilic leucocytes in the peripheral blood fell to zero. Campbell noted cardiac hypertrophy to accompany acclimatization of mice (31). Killick studied acclimatisation to CO in mice and found that the compensatory mechanisms, indicated by polycythemia, expansion of blood volume and enlargement of the spleen, permitted the mice to endure, without symptoms, exposures to CO which affected the controls intensely (97). Gorbatow and Noro showed that acclimatisation of a crude sort could be attained by rats and mice without the development of polycythemia (66). However, Clark, Otis and Leung have demonstrated recently that mice acclimatised to low O_2 tensions were resistant to subsequent exposure to CO, and that, conversely, a cross-resistance to hypoxia was demonstrated in CO-acclimatised mice; in both groups of animals a comparable degree of polycythemia and increase in Hb had occurred (42). Lewey and Drabkin noted no evidence of acclimatisation in dogs exposed daily to CO (109). There is, in addition, the extraordinary report of Van Bogaert and coworkers who exposed a monkey to CO for an hour daily (17). At the outset 0.01 p.c. CO produced a COHb saturation of roughly 30 p.c.; six months later 0.15 p.c. was required to induce the same COHb saturation, a 15-fold increase. With respect to the degree of acclimatisation, Campbell has pointed out that although growth curves in rats may indicate complete adaptation to CO, nevertheless, reproduction is impaired (29, 33). Confirmation of this observation is reported by Suhrie and Miller (213). Acclimatisation, then, may be only relative and requires strict definition.

In the case of man there is ample indirect evidence which indicates that repeated exposures produce enhanced tolerance and acclimatisation (95). Killick has studied the problem of acclimatisation as it occurred in herself (96, 99). She has reported that exposures of 6-hours' duration at 5 to 8 day intervals over a 6 months period to concentrations of CO ranging from 0.019 to 0.045 p.c. induced acclimatisation indicated by the following: diminished symptoms, slightly less tachycardia, and the amazing finding that after acclimatisation the rate of uptake of CO was reduced by approximately one-third; there were no significant changes in the erythron. Determinations of M, the partition coefficient of Hb for CO and O_2, showed no change, and short-term closed circuit experiments gave

no support for the possibility that CO had been metabolized. The most recent hypothesis put forward to explain these remarkable findings is that "the lungs excrete or prevent the diffusion of CO" (99). There is no evidence by other workers, of which I am aware, which either confirms or refutes these fiindings. However, there is certain internal evidence in these reports which constrains the reader from accepting the concept until further work is forthcoming. The apparatus used for estimating COHb was the Hartridge reversion spectroscope; this instrument is suited admirably to certain determinations but is notoriously open to subjective errors. That some technical error might account for the unusual findings is suggested by the report that when the arterial pO_2 was calculated from the determined values of M and p.c. saturation of COHb, these tensions were found to *exceed* the alveolar pO_2 in 35 of 39 experiments by amounts varying up to 98 mm. Hg. In one experiment the determined alveolar air pO_2 was 93 mm. Hg and the calculated arterial pO_2 was 191 mm. Hg. In view of the overwhelming evidence that the alveolar structures act as inert membranes across which gases simply diffuse (117), it is difficult to accept the findings reported by Killick without reasonable reservations. It seems certain that acclimatization occurs; the mechanism responsible remains obscure.

RESPIRATORY AND CIRCULATORY EFFECTS

Haldane first pointed out that even when one third and more of the circulating Hb has been converted to COHb there was no significant increase in pulmonary ventilation (75). Chiodi, Dill, Consolazio and Horvath measured the ventilatory response in dogs and men during acute carboxyhemoglobinemia up to and over 50 p.c. saturation (36). No detectable hyperpnea was evoked and the CO_2 capacity and pCO_2 of arterial blood were unaltered. Asmussen and Chiodi studied the ventilatory responses of men with a COHb saturation of 20 to 30 p.c. during exercise which augmented O_2 consumption up to 2 l./min. (8). The ventilatory response was compared with those obtaining during inspiration of air and of a mixture containing only 10 p.c. O_2. The ventilatory volume during exercise after CO poisoning was the same as in the control measurement during breathing of air; in contrast, there was marked increase in ventilatory minute volume when the subjects breathed mixtures with a reduced pO_2. These studies have been confirmed fully (46). Such studies, and others in animals, indicate that the reduction in amount of Hb available for O_2 transport by the accumulation of COHb evokes no compensatory respiratory response. The probable explanation is to be found in the demonstration of Comroe and Schmidt that the carotid body of the dog is not stimulated by complete conversion of all Hb to COHb, *if* the pO_2 of blood perfusing the carotid is normal; the respiratory chemoreceptors respond to changes in O_2 *tension* but are insensitive to reductions in O_2 *content* (45). Other observations on animals have demonstrated a variety of respiratory responses to CO, but there were recognized complicating factors such as barbiturate anesthesia, shock of overwhelming anoxia, etc. (144).

The effects of CO on the circulation are manifold, to judge from the extensive observations which have been reported. It is difficult to be certain in many in-

stances whether the effects may be attributed to the specific action of CO or whether the changes noted are not secondary to prolonged anoxia. This important distinction cannot be made with any assurance, but in several cases general hypoxemia would appear to be the primary agent. In man, the conversion of 20 to 30 p.c. of Hb to COHb is accompanied at rest by slight and variable rises in heart rate and in cardiac output (8, 36, 99). When work is performed with this or lesser degrees of carboxyhemoglobinemia, however, the heart rate rises to considerably higher frequencies than those encountered during the control period of work, and cardiac output is augmented, as is ventilation (8, 36). At 50 p.c. saturation with COHb there is at rest a measurable rise in cardiac output of about 50 p.c. over the control value (8).

Arterial pressure in anesthetized dogs rises during the accumulation of COHb (144), although Brewer reported that acute inhalations of 10 p.c. CO in 90 p.c. O_2 produced no change in pressure (19). The response of carotid pressoreceptors was observed by Kayser who concluded that CO exerted no direct effect via this mechanism (93).

The effects of CO on structure and function of the heart have been the subject of many studies. The most recent study in animals was reported by Ehrich, Bellet and Lewey whose report furnishes, in addition, an extensive bibliography of earlier observations (52). Earlier, Christ had noted disseminated myocardial necroses in guinea pigs (38) and Gürich demonstrated extensive necroses in the hearts of two young persons succumbing to illuminating gas poisoning (70). Beck and Suter reported an unusually high incidence of angina pectoris in patients supposed to have undergone prolonged exposure to CO (14). Whether the association was real or fortuitous was not established beyond doubt. The anticipated variety of electrocardiographic anomalies, such as arrhythmias, S-T segment changes, etc. have been recorded in patients exposed to toxic concentrations of CO (52, 207, 208). Haggard studied the sequence of events leading to death in dogs exposed acutely to CO (71). He concluded that the primary failure was respiratory and that cardiac function was undisturbed if respiration was maintained artificially. However, von Oettingen's group noted that dogs developed secondary cardiac failure several hours after the CO had been eliminated (144). Schwerma and his colleagues emphasize that their observations of dogs poisoned to an extreme degree lead to the conclusion that "the condition of the heart is paramount for survival" (187).

Various types of exposure to CO were studied in dogs by Ehrich and coworkers (52). Daily exposures which produced 20 p.c. COHb and acute exposures resulting in 40 p.c. COHb were followed by microscopic degenerative changes in myocardial fibers and by inversion of T waves and elevation of S-T segments in the electrocardiogram. Whether these findings may be applied *in toto* to man is conjectural, especially since these workers found that other control dogs exposed discontinuously to 10 p.c. O_2 similarly developed myocardial changes of like degree. Elevation of COHb saturation to more than 75 p.c. for one hour resulted in more extensive myocardial necroses and hemorrhages, with atrio-ventricular dissociation observed in the ECG.

von Oettingen has reviewed the literature which purports to establish a specific effect of CO on the entire vasculature (145). It may be summarized, in the opinion of this reviewer, as not proven. However, there is some suggestive evidence pointing to transudation of plasma water out of the vascular bed (9, 130). As will be discussed below there are certain special vascular beds, such as the cerebral, which would appear to respond to CO intoxication with a specific reaction pattern, but it would be difficult to establish that the basic reaction differs significantly from that induced by several forms of hypoxemia. The clinical reports of vascular occlusion with gangrene (54) or early formation of decubitus ulcers (157) are interesting observations, but in view of the age of some of the patients or the severity of the intoxication it is difficult to ascribe these changes to any special action of CO.

The response of the spleen and its role in CO intoxication were the subject of a series of studies in Barcroft's laboratory (11, 12, 16, 78). The blood in the splenic pulp, lying in a stagnant backwash, takes up CO at a considerably slower rate than the general circulation. In response to CO intoxication the spleen contracts and adds fresh Hb to the peripheral circulation. This response is mediated neurally from the spinal cord and in certain animals may provide some measure of compensatory defense; for example, splenectomized guinea pigs succumb sooner to CO than their normal controls, yet HCN kills both groups at the same rate.

In summary it may be said that although the immediate compensatory responses of respiration to lowered pO_2 are considered generally to be sluggish, nevertheless they are brisk in comparison with the responses to CO. Local damage to critical structures such as the myocardium appear to be easily induced by CO, and this may be related to the high level of continuous work output by an organ requiring very large amounts of O_2. The effects of CO on cardiovascular structures do seem to be more than the results of simple anoxemia but the case is not proved.

Peripheral and central neural effects

Function of peripheral nerve is susceptible to gross impairment by exposure to high partial pressures of CO. Schmitt first demonstrated the depression of action potential in peripheral nerve and linked it with an inhibition of respiration (179). Then later, with Beck (180) and with Gasser (181), he described the rise in threshold and fall in after-potential induced by CO. These effects were reversed promptly by intense illumination, which by analogy with the effect of light on the affinity of hemoglobin for CO, suggested than a heme-like respiratory pigment was poisoned by CO. Arvanitaki and Chalazonitis studied the effects on the spike-potential of squid nerve of a variety of respiratory inhibitors (7). Of particular interest in this study was the finding that replacement of air by pure CO in the ambient environment lowered the potentials abruptly in the course of a few seconds; pure N_2 had no discernible effect during short periods, whereas pure O_2 enhanced the potentials. Wright measured both action and demarcation potentials as well as threshold in mammalian peripheral nerve and noted inhibitory effects of both N_2 and CO; in some cases the CO was more

effective (234). Haggard found that the growth of the neuroblast was uninhibited in an atmosphere of 79 p.c. CO and 21 p.c. O_2; however, provision of CO in the form of illuminating gas blocked growth (72). In addition to these studies there are clinical descriptions of extensive peripheral neuritis occurring soon after intense CO (and illuminating gas) poisonings (24, 103, 175, 229).

Hedinger has discussed clinical examples of CO poisoning in which there developed local muscle paralysis associated with swelling and pain, with eventual progression to permanent contracture (80). Biopsy study revealed early necrosis, followed by fibrosis and calcification. These changes were interpreted to be the end results of vascular disturbance rather than a specific lesion of the muscle.

The literature dealing with the lesions and functional disturbances produced in central nervous system structures is vast. The general review of histopathology of the CNS resulting from central anoxia compiled by Hoff, Grenell and Fulton will furnish selected references to a large portion of the earlier and recent reports (83). A review of the literature cited by Hoff *et al.*, and other communications to be noted here, leads one to the conclusion that most authors attribute the lesions produced by CO either to vascular influences or to direct neuronal damage or to both. Careful search will reveal reports that will attest to the appearance of almost every recognized neurological or psychiatric syndrome following severe CO intoxication. More recently the Scandinavians have reported disturbances of vestibular and auditory systems which they attribute to CO (125, 143, 158, 174, 198, 214).

There is impressive evidence that CO produces selective and severe damage to localized areas of the cerebral vasculature. The cornu ammonis of the hippocampal cortex of the opossum exhibits exquisite sensitivity to generalized poisoning by CO. Scharrer, who has studied this phenomenon, has showed that other cerebral areas show no histological damage until there has been repeated, intense exposure, after which diffuse changes develop (177). He attributes the localization purely to the special form of terminal circulation which supplies this particularly vulnerable area: the usual dichotomizing arterial branching has been replaced by a long vessel which gives off single branches as it diminishes in size, and the cornu ammonis is irrigated by the terminal branches. The structural relations are such that any fall in the *vis a fronte* on reduction in general arterial pressure will impoverish this area selectively. In man, the commonest area for the development of localized damage is the anterior portion of the globus pallidus, the lesion of Kolisko (102); and several observers have concluded that primary vascular damage is the basis of this and other more diffuse lesions (55, 110, 210). There are a number of experimental investigations on animals which may be interpreted, on the basis of edema, capillary dilatation, and rise in cerebrospinal fluid pressure, to indicate profound alterations in the integrity of cerebral vessels (37, 59, 131, 144, 199). Associated findings have been the appearance of permeability of the choroid plexus to the passage of Trypan Blue and Congo Red (196, 209); this occurrence has been denied by others (69).

Other lesions are less easily attributed to vascular damage alone. Stewart early noted the extensive cortical damage which followed severe CO poisoning

(210). Profound demyelinization (88, 90, 226, 230), inflammatory foci (4), cortical atrophy with ventricular dilatation (107), localized damage to paraventricular nuclei (67), diffuse striatal damage with Parkinsonism (68, 135, 136, 159, 190)—all these and various combinations have been discovered in clinical pathological material. A more recent study by Lewey and Drabkin employed dogs who were gassed for 6 hours daily over an 11-week period (109). The p.c. of CO in inspired air was 0.01 and the blood saturation of COHb averaged 20 p.c. At the end of the period all the dogs walked stiffly on a wide base, and 4 of the 6 were unable to walk on their hind legs when the fore legs were supported. Pathological examination 3 months after gassing revealed no lesions in peripheral nerves, but there were scattered cortical infarcts and diffuse alterations in both granular and pyramidal layers. The globus pallidus and entire brain stem were mottled with "mild anoxic necroses." The extent of demonstrable microscopic disease with this degree of CO poisoning is surprising in the extreme, and the findings should be transferred to man only with the utmost caution.

The only attempt to discover a biochemical lesion in central nervous tissue associated with severe CO hypoxia is that reported by Rosenthal and his collaborators (163). Brain suspensions from animals poisoned severely with CO respiring in pyruvate and glucose substrates exhibited the same activity as the controls.

Shillito, Drinker and Shaughnessey determined that in metropolitan New York in a ten-year period there were 21,000 cases of CO asphyxia (195). During the same period 1 in 2000 admissions to psychiatric hospitals was for the treatment of psychoses secondary to CO poisoning. The most common reaction pattern has been found to be confusion, disorientation, loss of judgment and memory (162). The reaction is noted immediately in two thirds of the cases but its onset may be delayed for several weeks in others (195). Others forms of disorders of cerebral and mental function have been described (2, 3, 18, 44, 64, 82, 104, 133, 134, 141, 225, 228).

A review of this complex field leads to the conclusion that nervous tissue, particularly central, is especially vulnerable to damage during CO intoxication. There is evidence that the effects stem from combined vascular and specific neuronal damage, but the mechanisms which operate are not defined, and, indeed, some would appear to be common to all agents which lead to anoxia generally in the central nervous system.

Special effects of CO

There have been recorded a number of observations on the effect of CO on special systems. They have not lent themselves to easy incorporation within the general phases discussed above, and are presented below in fragmentary fashion.

Blood

There is an extensive literature pertaining to the development of polycythemia and anemia in men exposed to CO. The references to this information have been

compiled by Brieger who recently has studied the effect of repeated acute CO intoxication on the erythron of the dog (20). Some dogs developed transient polycythemia, some anemia; one dog developed permanent polycythemia. In all, the appearance of reticulocytes and normoblasts in the peripheral blood indicated that bone marrow had been stimulated. The pattern of response would seem to be the same qualitatively as that seen during adaptation to hypoxia.

Despite reports to the contrary, CO would appear to exert no significant effect on blood coagulation (60), activity of tissue thrombokinase (161) or the fragility of erythrocytes (132).

Endocrines

Several specific alterations in a number of endocrine organs have been attributed to CO. All these reports antedate the present concept of the close functional interrelations of these organs and of their profound structural and functional responses to a variety of environmental or internal stresses. An interpretation of the reports noted below made in the light of newer understanding would suggest that in general the changes were not specific.

Acute hyperthyroidism following exposure to CO has been described, examples of which have been recorded by Raab (156) and by Baader (10). Kampelmann and Schulze (91) and, in a similar investigation, Linnemann (124) found that repeated exposures to CO produced in guinea pigs anatomical evidence of increased activity of the thyroid and evidence by bioassay of hypophyseal depletion of thyrotropic hormone.

Patterson, Smith and Pickett gassed rats with illuminating gas daily for several months (153). They reported reduction in weight of testes and reduction in number of spermatozoa; the hypophysis became basophilic and "castrate" cells appeared together with increased elaboration of gonadotropic hormone. Schmelser recorded the last of a series of German studies on the various effects of acute and chronic CO poisoning on the adrenals (178).

Gastro-intestinal

Patterson and coworkers found that food intake and gastro-intestinal motility were inhibited by repeated exposure to CO (152). This reaction might have been responsible to some extent for the endocrine changes noted immediately above. Walther reported that acute intoxication with CO produced in rabbits no alteration in gastric secretion, but that on microscopic examination there were noted mucosal erosions, hemorrhages and edema (222).

Metabolism

Clinical reports are studded with isolated observations of hyperglycemia and glycosuria during severe CO poisoning (138). Smith and Penrod found that albino rats responded with a hyperglycemia which was a linear function of the COHb saturation (201). There was no accompanying alteration in either insulin or glucose tolerance. Schulze found that in mice the hyperglycemia induced by CO was accompanied by depletion of glycogen stores of the liver (185). He

suggested that exposure to CO stimulated a quick adrenal component and a slower thyroid component of these so-called compensatory mechanisms.

There are two sets of observations on overall metabolism which are not easily reconciled. Walters found that rats exposed to as little as 0.02 to 0.05 p.c. CO responded over a period of 4 to 6 hours with a fall in body temperature and a moderate decrease in the amount of CO_2 produced (221). Reploh, using rabbits and a higher concentration of CO, found that the same slight fall in CO_2 production but also a rise in O_2 consumption (160). This same fall in respiratory quotient might explain Walter's findings.

Campbell found that carcinomata implanted in mice underwent a remarkable retardation in growth rate when the mice were exposed continuously to atmospheres containing up to 0.28 p.c. CO (30, 32). No such effect was noted in the case of transplanted sarcomata. The most likely explanation is one suggested among others by the author, that the tumor shared in the depression of a host of functions, all impaired by the high degree of CO poisoning.

There is little internal evidence to establish that the various scattered observations noted in this section are owing to a specific effect of CO and not to the general actions of hypoxia from whatever cause.

Resuscitation and treatment

The literature relating to treatment of asphyxia has been bitterly polemic for many years. The specific treatment of CO poisoning is part of that more general problem and has had its share of controversy. The basic problems are agreed on by all, that the main aims of therapy are determined by the fundamental principles discussed above in the consideration of uptake and elimination of CO. Increased pulmonary ventilation and a maximum safe rise of inspired pO_2 combine to hasten the dissociation of COHb and excretion of CO. The need for rapid intensive treatment is emphasized in studies such as that of Van Amberg who found that permanent residual disturbances in mentation did not occur if the period of coma was less than one hour (217). The controversies have revolved about the optimal means of increasing and supporting respiration, and about the usefulness of several chemical and physical agents reported to protect from CO and to speed recovery.

There is no need to recount here the experimental evidence and reasoning which led Henderson and Haggard to propose, support and popularize the use of 5 to 7 p.c. CO_2 in O_2 ("carbogen") as an inspiratory mixture to be supplied in conjunction with manual or mechanical artificial respiration (139). This mixture is widely used and it has been accepted generally as the best available form of immediate therapy. Recently, however, Schwerma and coworkers have reported on the results of an extensive investigation of various forms of resuscitative maneuvers used in dogs gassed with either illuminating gas or commercial CO (187–189). The gist of these studies is that if the dog is gassed until the development of gasping respirations, when death will supervene in a matter of a few minutes, then the survival rates are the same whether 7 p.c. CO_2 in O_2 or 100 p.c. O_2 is supplied by artificial respiration. They concluded that CO_2 was "an

unnecessary therapeutic adjunct". It should be pointed out that no conclusion can be drawn as to whether these findings can be applied wholly to lesser degrees of CO intoxication in man. End and Long have made the interesting observation, which is readily reconciled with the known relations of CO, O_2 and Hb, that guinea pigs recover much more quickly from CO intoxication if placed in an O_2 environment under a pressure of 3 atm.[1] (53). Koch has reported favorable therapeutic results from the use of modified exchange transfusions (101). Obviously great care must be exercised to avoid additional stress on the cardiovascular mechanism.

Brooks has reported on several occasions that methylene blue injected into rats and rabbits intensely poisoned with CO produced an unusually rapid recovery (21–23). The presumable rationale for the use of this redox dye is that it acts in the stead of intrinsic systems to accept hydrogen electrons and thus maintain some semblance of normal oxidative processes. Appealing as this hypothesis may be, nevertheless the experimental data are open to certain question. Haggard and Greenberg have marshalled the evidence which throws into some doubt the use of methylene blue (73); and Sturm and Wohlfarth found no benefit in the use of a proprietary combination of glucose with methylene blue (212).

Cameron has reported a series of inexplicable observations which would indicate that total body irradiation by X-ray hastened recovery from CO poisoning in experimental animals (25, 26, 28). Thurnherr observed slowing of CO uptake and hastening of elimination with quartz light irradiation (215).

The most recent addition to the therapeutic armamentarium is the intravenous injection of procaine (3A). No controlled studies in experimental animals have been reported but the clinical observations are provocative. The rationale is empiric and no convincing explanation for the dramatic effect of procaine on damaged CNS function has been proposed.

Summary

In the recent years steady progress has been made in filling in the details of well-grounded concepts of the action of CO; and newer observations have led into unexpected developments. A wide spectrum of biological processes not dependent on hemoglobin have been found to be impaired by CO. Skeletal and cardiac muscle, and the intact animal as well, have been shown clearly to possess the capacity of oxidizing CO to CO_2. The basic relations of CO, O_2 and Hb both in static and dynamic systems have been explored with profitable clarification of the fundamentals. More precise measurements are available now to define those factors which modify the rate of uptake and elimination of CO in man. The higher resolution of technics for assessing function in man have provided evidence of the impairment produced by small amounts of CO. The phenomena associated with acclimatization have been under study but the mechanisms are unexplained. A large number of special systems are altered by exposure to CO,

[1] A study of this phenomenon in man has just been reported (155A).

but in many it is not clear yet whether these effects are specific for CO or rather simply general reactions to any restriction in the normal delivery of O_2 to tissues. Therapy available for CO poisoning is based primarily on the fundamental relations of CO, O_2 and Hb.

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