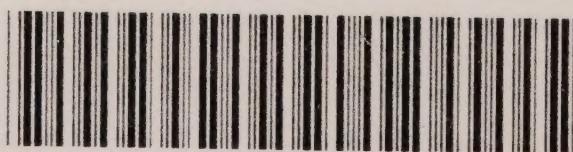
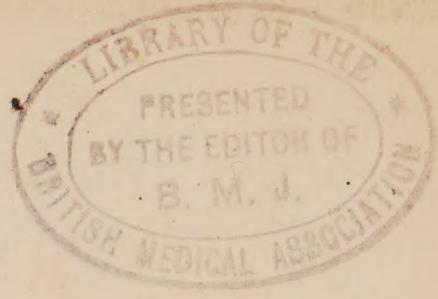


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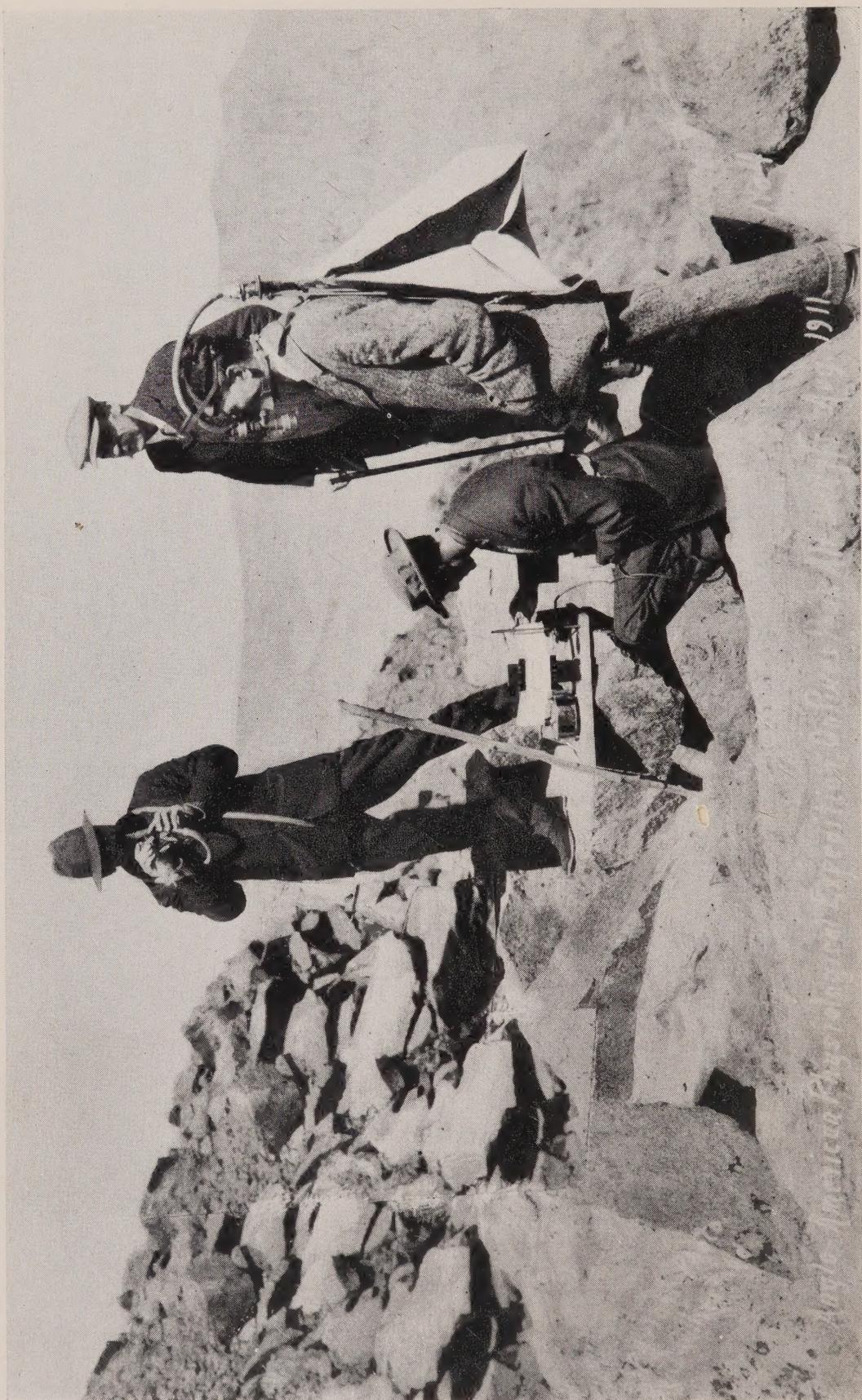
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Adventures in Respiration



The Pike's Peak Expedition of 1911: Douglas wearing a "Douglas bag" to collect expired air for the determination of the amount of oxygen consumed during climbing; Haldane standing back of him; Schneider kneeling and recording his respiration; Henderson taking samples of alveolar air.

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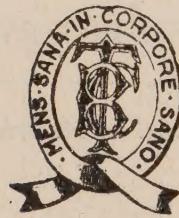
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Adventures in Respiration

MODES OF ASPHYXIATION
AND METHODS OF RESUSCITATION

By

Yandell Henderson



"Over the oxygen supply of the body carbon dioxide spreads its protecting wings," — Miescher, 1885.



LONDON

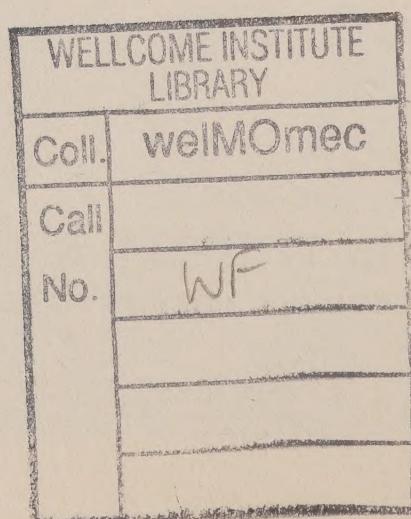
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*To the Memory
of
John Scott Haldane*

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Introduction

A METHOD of revival from carbon monoxide poisoning and other forms of asphyxia has now come into wide use. It consists in the inhalation of carbon dioxide diluted with air, or oxygen. When this method of revival was introduced by Dr. Howard W. Haggard and myself seventeen years ago, it appeared so much at variance with current opinion that extensive discussion of its scientific basis would have aroused more opposition than support: a risk against which an earlier experience had warned me.

More recently this method of revival has demonstrated its capacity to save the lives of a large proportion of the babies who now succumb to the asphyxia and narcosis of the newborn. It is already saving many, and its use is constantly extending. This fact is the more significant because it directly contravenes an almost universally accepted scientific doctrine: the biochemical dogma of acidosis.

Thirty years ago I put forward the view that acapnia is a factor in the depression of vitality after anaesthesia, surgical operations, physical injuries and severe illness. Acapnia is a deficiency of carbon dioxide that leads in turn to a deficiency of oxygen also. For fifteen years I campaigned for this theory vigorously, but quite unsuccessfully. It is now generally forgotten or else referred to only as "one of the disproved and rejected theories."

What I could not achieve by the first fifteen years of direct advocacy has now, nevertheless, been won by a manoeuvre as old as the Trojan horse. This success is the result of another period of fifteen years in which, avoiding theoretical discussion, I have devoted my efforts mainly along practical lines. As a result cylinders of carbon dioxide, or carbon dioxide diluted with oxygen, are now part of the equipment of nearly every surgical

operating room; and an inhalation of these gases is commonly administered at the termination of anesthesia. For practical purposes the acapnia theory has won its way into surgery in those cylinders of carbon dioxide.

As the result of these diverse lines of practical effort, the same means are now employed to restore vitality and prevent pulmonary complications after surgical operations as those by which asphyxial babies are resuscitated, and the victims of carbon monoxide poisoning are revived. And it is surely a fact of fundamental significance, that these conditions—so different in origin—are all effectually relieved by essentially the same means.

Beside these conditions there are many other states through which men die that, in their early stages, are curable with carbon dioxide. Among them are some forms of pneumonia. In final analysis they are all related to asphyxia. If this is so, it suggests further possible saving of life. From what has been achieved in resuscitation from asphyxia we may learn also how to counteract some—perhaps many—of these other modes of death.

Resuscitation from asphyxia is based upon the facts of respiration. These facts are simple and interesting; but the principles involved are recondite. On this account I have presented the facts with little theory or system as a simple story of adventures: adventures in respiration as I have myself experienced and enjoyed them. My excuse must be that in much of what is here described I have explored a new region; and that it is as difficult to systematize the evidence as for an explorer on an unknown coast, sailing in fog and storm, to draw at once a complete and accurate chart. There are indeed sailing directions for this region. They are afforded by the biochemistry of the acid-base balance of the blood as now generally accepted. But in fact

they only add to the difficulty; for where they warn of dangerous reefs I have found a clear passage, and by steering contrary to their directions, wreckage and loss of life have actually been diminished. At critical points their latitude and longitude are erroneous, and even the points of the compass are reversed.

In a great part of my investigations during the past twenty years, Dr. Howard W. Haggard has been closely associated. My debt to him is gratefully acknowledged.

Chapter I

OXYGEN AND CARBON DIOXIDE

ON THE morning of May 9, 1794, in the Place de la Revolution in Paris, Antoine Laurent Lavoisier died under the guillotine. The Republic, it was said, had no need of scientists.

One hundred and seven years later (1901) Michael Foster in his history of physiology wrote: "As the sharp stroke of the guillotine severed his neck there passed away from this world in his fifty-first year, this master mind of science, who had done so much to draw aside from truth the veil of man's ignorance and wrong thought; and there passed away too, the hope of his drawing aside yet other folds of that veil, folds which perhaps wrap us round even today."

A few years before his death Lavoisier had achieved one of the supreme feats of science. What Priestley, Black, Scheele and others had sensed dimly and partially, Lavoisier showed clear and complete. He had demonstrated the nature both of combustion and respiration: a fundamental likeness between fire and breathing. It is oxygen, both in combustion and in respiration (in its broadest sense), that unites with carbonaceous matter, liberates heat, and produces carbon dioxide.

From this fundamental conception have come far reaching practical applications and an understanding of the unities of Nature that is even more important. We can now measure the energy expenditure of the body by determining the amount of oxygen consumed. We can compare, as Lavoisier suggested, the combustion in the working muscles of a laborer and the reasoning brain of a scientist. We see that respiration is almost

life itself; yet not quite, for we find that thought is not merely physical energy.

The lessons of this vast conception are not limited to normal life. They tell us also of the processes involved in dying. As exclusion of oxygen extinguishes a fire, so too in a man or animal a deficiency of oxygen in the blood and tissues induces death in asphyxia. We have learned to regard the circulation of the blood as essentially a part of the machinery of respiration. The blood carries oxygen from the lungs to the tissues and organs of the body, and carbon dioxide from the tissues and organs to the lungs. It is in the tissues and organs therefore that the fundamental process of respiration occurs. Death is the cessation of that process. There are many modes of dying that bring men to their ends; but only one final common cause. Whether the brain is destroyed, or the lungs blocked, or the heart stopped, death finally occurs in but one way only. When breathing and the heart come to a standstill, the supply of oxygen to the body ceases. Unless a man is burned alive, the tissues of his body always die of asphyxia.

THE PROBLEM OF ASPHYXIA

It is only when we ask the question—"What then is asphyxiation?" that a "fold of the veil of wrong thought" hides from us the truth, and hides even the nature of our ignorance. Asphyxiation is the process that occurs whenever it becomes difficult for the tissues to obtain their normal supply of oxygen. Any absolute deficit kills quickly. So much we know. But unwiseley we generally fail to realize that this is nearly all that we know. The habit of our minds makes it difficult for us to accept the mere lack of something—in this case oxygen—as the cause of a far reaching effect. It is more satisfying to have a positive cause,

and so it came to be believed, and to be stated in text books and works of reference, and to be taught—and it still is taught—that the cause of asphyxiation is carbon dioxide.

In science a mere habit of thought, often erroneous, comes to be accepted as logic. To discover new truth we have to break that habit of the mind. Generally we merely argue from one set of conditions that we think we understand, to another that we suppose is similar. Drowning, strangling and suffocation under a pillow, in a grave or in the uterus, all stop both the intake of oxygen and the outgo of carbon dioxide. Therefore, it was inferred, an accumulation of carbon dioxide must be as much the cause of death as a deficiency of oxygen. It even came to be assumed that a deficiency of oxygen kills by producing an excess of carbon dioxide. Two facts were overlooked. One is that without oxygen, carbon dioxide cannot be produced. The other fact is that in all the most important forms of asphyxiation (e.g., carbon monoxide asphyxia), while the supply of oxygen is restricted, the elimination of carbon dioxide is still entirely free, or is even abnormally augmented. Asphyxia involves deficiency of oxygen, and generally deficiency of carbon dioxide also.

Nevertheless almost down to the present time carbon dioxide has been regarded as par excellence the asphyxiant gas. No “fold of the veil of wrong thought” has hidden any feature of respiration more completely than has this conception of the part of carbon dioxide in asphyxia. Only a few years ago nothing would have seemed more improbable, or more illogical, than that inhalation of carbon dioxide, mixed either with oxygen or air, should ever be employed for the resuscitation of the victims of asphyxia. Yet such inhalation has now become the accepted treatment; and in the light of present knowledge it is entirely logical:

MOUNTAIN SICKNESS

The first indications of a change in the conception of asphyxia came less from science, or medicine, than from sport. In the eighteenth century men saw little beauty in mountains and took no pleasure in climbing them. But in the nineteenth century mountaineering became a major sport. When Saussure made the first ascent of Mont Blanc in 1788 he described not only the physical hazards of the mountain but also the effects of the rarefied air; the breathlessness, muscular weakness, nausea and extremely rapid heart beat. He and others laid great stress also upon the occurrence of hemorrhages. Knowing that the pressure of the atmosphere is greatly reduced at altitudes, and that the blood in the arteries is normally under a considerable pressure, they supposed that the blood vessels might even burst.

That which they expected they saw. One writer, with a style more colorful than accurate, reported that while crossing the Andes on a mule, he had walked for a time to rest the animal. Under this exertion his breathing became greatly oppressed "his eyes bulged and his lips burst." Yet as we now know the blood vessels are in reality under no more strain at a great altitude than at sea level. When the air pressure upon the exterior of the body and in the lungs is diminished, a part of the gas, especially the nitrogen dissolved in the blood, rapidly diffuses out; and the gas pressures within and without the blood vessels again become equal as at sea level. Yet the idea is still common that hemorrhages occur under low barometric pressure.

The first long step towards a correct explanation of the effects of low barometric pressure on man was taken by a brilliant Frenchman, Paul Bert, in the seventies of the last century. He demonstrated that the effects were entirely due, not to the lowering of the air pressure as a whole, but to the decrease in the ab-

solute amount of oxygen—the so-called “partial pressure.” He found that he could induce practically all of the symptoms of mountain sickness by placing his subjects, men and animals, in a steel cylinder and pumping out a part of the air. When the pressure within the cylinder was reduced to about one half that of the normal atmosphere, marked effects were induced—such as panting, dizziness and muscular weakness—and if the pressure were lowered further, unconsciousness. When, however, the air in the cylinder was replaced by pure oxygen, the pressure could be reduced almost to ten per cent of atmospheric pressure before the subjects manifested these symptoms. As the amount of oxygen contained in an atmosphere of pure oxygen at a tenth of an atmospheric pressure is about the same as in air (which is only one-fifth oxygen) at half an atmosphere pressure, these observations indicate that the oxygen supply alone is the factor involved.

The application of these observations to conditions in the high Alps came in the last decade of the nineteenth century. Zuntz, a professor of physiology in Berlin, was an enthusiastic mountaineer. He and his associates both climbed to great altitudes and investigated the effects upon themselves of the rarefied air at those altitudes. Following the ideas of Paul Bert, they concluded that the effects of altitude are not due to the diminished mechanical pressure of the air upon the surface of the body and in the lungs, as earlier investigators had supposed. They are due, instead, to the fact that, as the barometric pressure falls with each increase of altitude above sea level, the pressure of oxygen diminishes proportionally. Mountain sickness is a form of asphyxia.

At about the same time, Mosso, a professor in Turin, and his pupils also climbed the Alps, and made observations on them-

selves—their respiration, arterial pressure, and the disturbances of intellect and temper that great altitudes often induce. But they reached a quite different conclusion. Mosso said that mountain sickness is mainly due to an excessive loss of carbon dioxide; and for the condition, which he supposed to be thus induced, he coined the word “acapnia” from the Greek word “kapnos,” meaning smoke. Literally, acapnia means smokelessness.

Out of this disagreement there arose a fine scientific dispute: each side trying to show that the other was wrong. And yet, as we now know, and as is often the case in scientific disagreements, each side was right to the extent that each had demonstrated an important fact. Oxygen deficiency, as Zuntz held, is certainly the cause of mountain sickness; but it is far from being the sole condition. It induces many other conditions; and these others are not immediately relieved and reversed by restoration of an ample supply of oxygen. One of these conditions is the acapnia, or deficiency of carbon dioxide, which Mosso had discovered.

Yet Mosso made a serious error; for he supposed acapnia to be due to the direct effect of diminished air pressure—a mere diffusion of carbon dioxide out of the blood in the lungs, like the diffusion of carbon dioxide out of soda water after the bottle is opened. Certainly such diffusion is not the cause of mountain sickness nor of acapnia. And yet, no matter how it is induced, acapnia is certainly one of the most important conditions involved in mountain sickness.

Thus already there appeared a relation which we shall meet again and again in this book in every form of asphyxia, even in the fetus in utero, and not only in asphyxia, but also in such related conditions as hemorrhage, postoperative depression and

anesthesia. We shall find that a diminished supply of oxygen in the lungs and blood always induces a diminution of the content of carbon dioxide also by overbreathing and in other ways; and that not only does a deficiency of oxygen induce acapnia, but that acapnia in turn tends to intensify the deficiency of oxygen; for it depresses respiration and renders the blood less ready to give up oxygen in the tissues.

This relation between anoxia and acapnia is thus the heart of the problem of asphyxia. And yet, lest I should mislead the reader, let me say at once that in my opinion we really have not even today solved the problem of the inner nature of the relation of anoxia and acapnia. What we do know is mainly the very practical fact that, with few exceptions, when anoxia has produced asphyxia, recovery is vastly promoted by counteracting, not only the anoxia by administration of oxygen, but also the acapnia by administration of carbon dioxide. The body needs oxygen, but it needs carbon dioxide also—normally the carbon dioxide that the body itself produces. It is true that even a rather acute acapnia may be in time overcome by the gradual reaccumulation of carbon dioxide in the blood and tissues, provided that the oxygen supply is ample. On the other hand, there are conditions due to a prolonged deficiency of oxygen that are effectively counteracted by administration of carbon dioxide diluted in air, but from which, owing to an extreme depression of respiration and the circulation, sufferers would not recover if oxygen alone were administered.

These facts may be roughly summarized in the statements that oxygen is an essential food, but not a stimulant. Carbon dioxide, on the contrary, is a tonic and a stimulant: a stimulant that now annually saves thousands of lives.

Chapter II

SHOCK AND ACAPNIA

IN THE second half of the nineteenth century Germany was preëminent in chemistry and the medical sciences. Every young American physiologist aspired to round out his education by a "year in Germany." There he experienced the masterly neglect of the German professors, and learned that in order to pluck the fruit of learning from the highest branches, one must climb the tree all by oneself, even if it is a tree that no one has ever climbed before.

In the autumn of the year 1900, I returned from the conventional "year in Germany." There, as in four years previously in America, I had devoted myself chiefly to the chemical side of physiology. At home I met my "tree" immediately, for the job to which I came was to teach the other side of physiology, and of that side I knew next to nothing. From an investigator's standpoint I had the great advantage that I came to the subjects of the circulation and respiration with an entirely open mind.

I taught, as everyone then did, that respiration is chiefly controlled by the vagus nerves and is relatively little influenced by oxygen or carbon dioxide. My ignorance in regard to respiration was disturbed by no doubts. But in lecturing on the circulation I had the uncomfortable feeling that such a hydraulic apparatus as I described simply would not work. In particular I had to admit to myself, even after a long summer vacation devoted to an intensive study of Tigerstedt's *Lehrbuch des Kreislaufs*, that I had no clear idea—and I suspected that no one else had—as to how the heart is filled between strokes. Certainly

the heart can discharge into the arteries no more blood than comes to it through the veins. Clinicians and physiologists alike spoke of increased or decreased "heart action"; but with no clear understanding as to how the heart is supplied with the blood that it pumps, and how that supply is controlled. It was accepted as a sufficient explanation that the pressure of the blood in the arteries drives it on into the veins. But was this "vis a tergo" all that was involved? Was the venous supply unlimited? When the circulation was failing, was it the heart itself that failed?

THE VENOPRESSOR MECHANISM

In order to satisfy my own mind on these questions, I constructed from a child's large rubber ball a chamber that could be slipped airtight, but without compression, over the ventricles of the heart of a dog. This simple cardiometer was connected by a wide rubber tube to a large tambour made out of the tin top of a tobacco jar. With this extemporized equipment, writing on one of the only two revolving drums that the laboratory possessed, I recorded the volume curve of the heart. (Later I used a proper tambour, 10 cms. in diameter, so constructed that the pressure and resistance were the same at all points in the stroke).

It was nearly 300 years since William Harvey had published his book "On the Motion of the Heart and Blood in Animals"; and in those years no other field of science had been investigated more intensively than the circulation. Yet almost the first volume-curve that I obtained showed a new fact: a small fact to be sure, but one with far reaching consequences. The series of events that follow each other, and are continually repeated, in each heart beat—the so-called "cardiac cycle"—was still described essentially in Harvey's words: "The contraction of the

auricles—the smaller chambers of the heart—fills the ventricles—the great chambers; and the ventricles then by their contraction, or systole, force the blood on into the arteries."

The heart does beat in this manner in a frog, in which animal it is most easily observed: alternately one chamber contracts in systole while the other relaxes in diastole. But in the heart beat of a dog the volume-curve showed a different relation. Instead of the ventricles being filled by the systole of the auricles, which

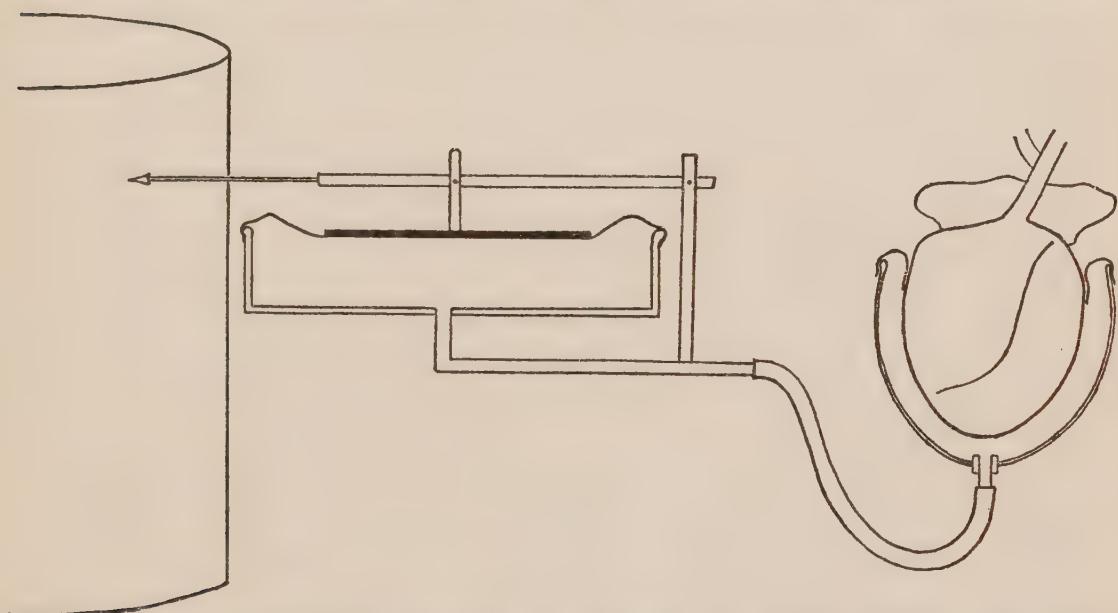


FIG. 1. Cardiometer and tambour for recording the volume curve of the heart. (For special construction of tambour, see Am. J. Physiol., 1906, 16, 335 and 1913, 31, 293.)

occurs immediately before that of the ventricles, these greater chambers were found to be nearly or completely filled before auricular systole occurs. In a slow full beat there is even a pause, which I called "diastasis," between this filling and the succeeding auricular contraction, and the auricular systole then adds little, if at all, to the distention of the ventricles. Auricular systole is chiefly important mechanically in that it aids in closing the valves.

What could be the factor that thus induces a rapid refilling of the ventricles immediately after each systolic discharge? Evidently it is the volume and force of the stream of blood through the veins to the heart. And to the unknown factor that controls this "venous return," and thereby largely determines the volume of blood that the heart can pump, I gave the name of the "venopressor mechanism." The importance of this factor in the circulation immediately appeared; for whenever it failed, the supply of blood through the veins to the heart was diminished, and in consequence the volume of the arterial blood stream also. Here, then, was what had always previously been called a "failing heart." But the failure of the circulation was evidently due, not to failure of the heart itself, but to failure of the "venopressor mechanism." This type of failure of the circulation is most easily induced by hemorrhage. It is the outstanding feature of surgical shock, as will be further shown in chapters XIV, XV and XVI.

Thus far all was clear. But beyond all was dark; for twenty-five years more of continuous searching were to pass before I could develop a clear mechanical conception of what the "venopressor mechanism" is. And this was the more disappointing because I had early reached the conviction that it is through failure of this factor in the circulation that the large majority of all deaths occur. If one could only find out what it is that normally maintains the venous return, and how it fails in physical prostration, it should be possible, I thought, to save, or at least to lengthen, innumerable lives.

Ever since Claude Bernard discovered the vasomotor nervous system, the mechanics of the circulation had been considered to involve only two major mechanical factors: the heart action and the peripheral resistance of the finer vessels of the arterial system

under the control of the vasomotor system. Goltz, in an experiment as celebrated as it was simple, had shown that slapping the abdomen of a frog—a sort of solar plexus blow—causes a relaxation of the blood vessels of the stomach and intestines and a depression of the circulation. The conception of arterial pressure (mistakenly called “blood pressure”) was then first coming into clinical medicine along with the use of the sphygmomanometer for the measurement of that pressure. Many writers of that day, flushed with this wonderful new conception, seem almost to have thought of the body, or at least of the circulation, as like a steam engine, and of a low arterial pressure as like a low pressure of steam in the boiler.

Accordingly, when investigators began to study the problem of the depression of vitality that then often followed major surgical operations, they measured arterial pressure. And finding that “blood pressure,” as they called it, was decreased, they inferred that they had found the cause of surgical shock. This was the reasoning in Crile’s work thirty-five years ago, as it has been also in that of many other investigations since, and even down to the present time. Always they return to vasomotor failure: a conception expressed by a phrase long and widely used: “Shock is a hemorrhage into the veins.” Yet one has but to drop logic based on theory, and to use his eyes, to see that the veins, and especially the jugular vein, of a patient lying on his back before operation and those of an animal before experiment, are filled with blood; and that, after an hour under anesthesia and operation or experiment, the decrease of vitality and weaker circulation are correlated with empty and collapsed veins. The state of the jugular vein is the simplest and most direct index of the venous return. And the venous return is the basic factor—as it were, the fulcrum—of the circulation.

To the leaders of American physiology in those days these considerations had little appeal. They continued to treat as a single factor those elements in the circulation that, as I thought, in reality constitute two fundamentally different factors. One is the peripheral resistance of the arterial system; the other the condition, or conditions, that maintain and regulate the venous return.

Accordingly, when at the meeting of the American Physiological Society in December 1904 I reported my first observations, the President of the Society, then the dean of our profession, merely asked "If these things are so, why have the rest of us not seen them?" And when in the summer of 1906 I presented at the meeting of the British Medical Association in Toronto, Canada, a paper summarizing the observations in the foregoing and following sections of this chapter, the matter excited some little interest for a year or two and was then forgotten. Shock in the sense of circulatory failure continued to be considered as essentially vasomotor; and the venopressor mechanism as in some way controlled by the vasomotor nervous system.

FAILURE OF THE CIRCULATION

Almost at the beginning of the work on the volume-curve another discovery developed. The laboratory possessed a minimum of apparatus, and in particular none for artificial respiration. In order to permit the placing of the cardiometer over the heart, it was necessary to open the thorax widely. Under these conditions the lungs collapse and it was necessary to blow air into them, so as to keep them distended, as well as to maintain respiration. To meet these requirements we had only a leaky hand bellows, and the janitor, who worked that implement for me, was compelled to keep up a rapid succession of pulmonary inflations;

the lungs undergoing a considerable deflation between strokes. The overventilation was therefore tremendous—much greater than is possible before the chest is opened; and the animals quickly went into collapse and died. And the fact that was most striking was that the more energetic the janitor was with the bellows, the more rapidly the animals collapsed. Thus it appeared that an acute acapnia, simply from overventilation of the lungs, may cause failure of the circulation.

This observation, which was to prove the starting point for 30 years of work, appeared at first as merely an annoyance; for the animals often died before I could record the volume curves of their hearts. Fortunately developments in thoracic surgery in Germany at this time indicated a way out of the difficulty. It consisted in an arrangement (the Ueberdruckverfahren of Brauer) by which the animal breathed air from a gasometer under a pressure sufficient to keep the lungs expanded after the chest was opened. Natural breathing continued and artificial respiration was unnecessary. The animal breathed this air through a long wide tube; and by varying the size of this "dead space" the animal was made to rebreathe a greater or less amount of its own expired air. When little or no rebreathing was applied, the lungs were overventilated; acapnia developed, the circulation failed, and the animal soon collapsed in shock. With much rebreathing the carbon dioxide of the animal's body was conserved or could even be made to accumulate. And under these conditions the vitality of the animal, the volume of the venous return, a normal heart action, and full circulation were long maintained. I did not then realize, as I do now, that the acapnia in many cases was due, not so much to overbreathing as to the decreased production of carbon dioxide consequent on depressed vitality and lowered muscle tonus.

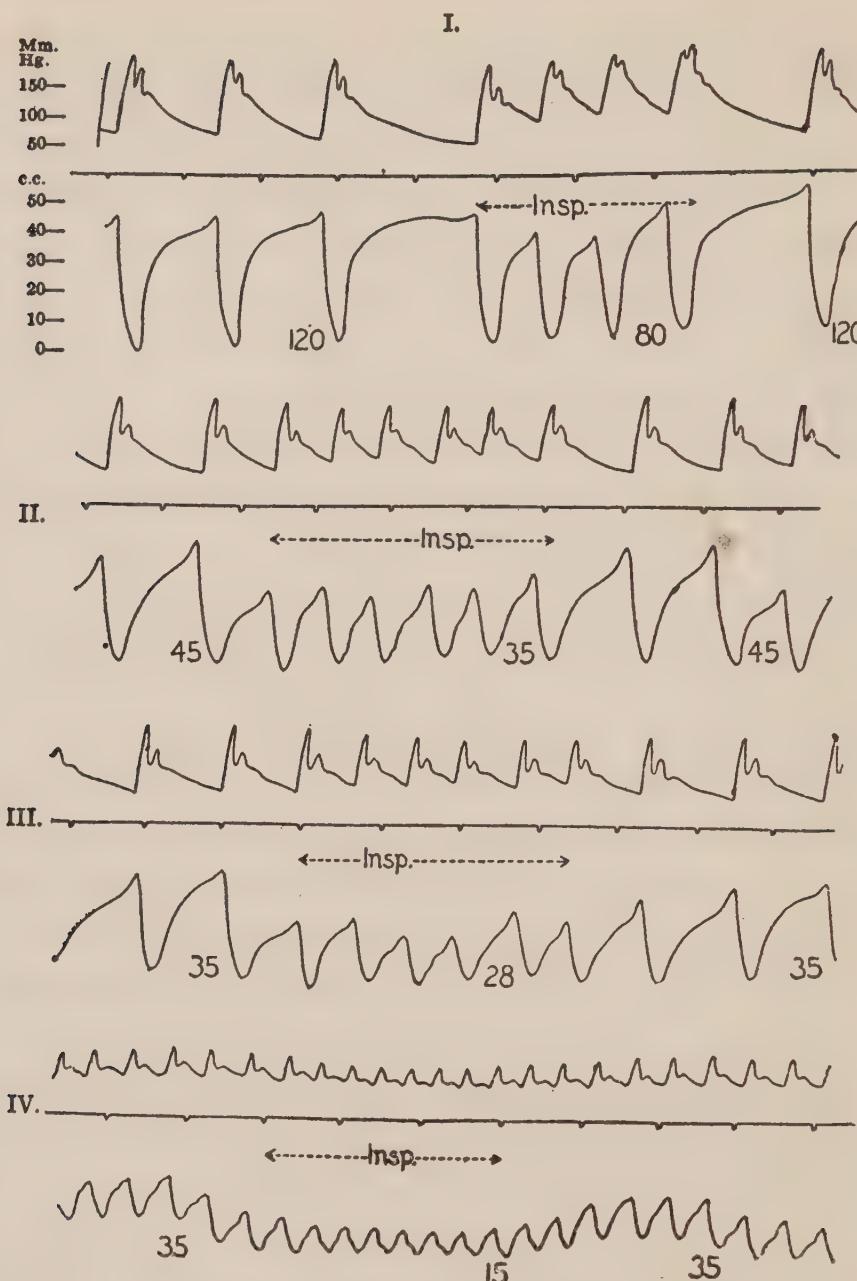


FIG. 2. Pulse curves, above, and volume curves of the heart, below. Auricular systole is the little spike just before the downstroke of the systolic discharge of the ventricles. The animal had received an intravenous infusion of saline, and was then subjected to a succession of hemorrhages, which induced a progressive failure of the circulation. The figures 120, 45, 35, 15, were the pressures in the jugular vein in millimeters of water. The variations in rate of beat were synchronous with respiration. Natural respiration of air at a pressure of 80 mm. of water was maintained. For full discussion see Am. J. Physiol., 1913, 31, 406.

From this beginning the use of rebreathing in connection with anesthesia made its way in a few years (between 1909 and 1919) into many surgical clinics and effected a notable decrease of anesthetic accidents and postoperative depression. It was a first step toward the control of the gaseous exchange that is the key to the control of respiration: a control that every capable anesthetist now maintains.

FATAL APNEA IN ANESTHESIA

My unorthodox conceptions of the circulation and of post-operative depression were received with incredulity. Physiologists would not accept an undefined "third major factor in the circulation" in which carbon dioxide may play a part. They stopped me with the question: "What is this factor?" And I could not answer. Accordingly I determined to avoid theory and to aim rather at introducing these ideas in practical form directly into clinical use. In this objective I received invaluable assistance—for which I can never adequately express my appreciation—from American anesthetists. But it is doubtful whether I could have succeeded had not J. S. Haldane and his collaborators, J. G. Priestley and C. G. Douglas, at the most convenient possible moment for me (1905), published their epoch-making studies on the part that carbon dioxide plays in the normal control of respiration.

I constituted myself therefore as an active propagandist for the Haldane doctrine, confident that the conception of carbon dioxide as a factor in the control of respiration must lead to recognition of a similar part in the control of other functions as well, and particularly of the circulation. But that recognition was long in coming.

Prior to the work of Haldane and his collaborators the move-

ments of the chest that we call breathing were considered to be regulated in the main by nervous reflexes. Chemical influences played a minor part, and opinion was still uncertain as to which of the two main chemical influences, oxygen or carbon dioxide, was the more important. The brilliant Swiss physiologist, Miescher of Basel, had assigned first place to carbon dioxide. But the full significance of carbon dioxide in the regulation of respiration became clear only with the work of Haldane, Priestley and Douglas. Variations in the oxygen content of the inspired air and in the air in the lungs, at least within moderate limits, were shown to induce little or no alteration in the volume of breathing. On the other hand, as they demonstrated, the regulation of the volume of breathing by carbon dioxide is so precise that normal respiration maintains a nearly uniform concentration of carbon dioxide in the air of the lungs. So precise, indeed, is this regulation that even a slight decrease in this so-called "alveolar carbon dioxide" automatically induces a temporary decrease or even a cessation of respiration: the so-called apnea vera. Their demonstration of the regulation of normal breathing by carbon dioxide was conclusive.

I undertook to extend this conception into the abnormal field, and in particular to analyze the problem of respiration under anesthesia. For this I was fortunately placed. It happened that, as my students then received no other instruction in experimental pharmacology, I had introduced as much of this subject as I could into my laboratory course in physiology. I believed—and I still believe—that no young doctor is really competent to administer anesthesia until he has been responsible—and has been duly rebuked—for causing a death under anesthesia: the death of a cat.

Cats were abundant. They are the most difficult of animals

to etherize with any degree of uniformity: far more difficult than a man. Unless uniformly etherized, these small and excitable animals pass quickly from the stage of incomplete anesthesia and excitement to that of profound narcosis and cessation of respiration; then as quickly back to excitement, and so back and forth, in and out of anesthesia. And with each alternation, disaster is approached more nearly. When at last it occurs, it generally comes, at least under ether, in the form of failure of respiration. Under chloroform it may come as Levy showed, in the form of ventricular fibrillation, i.e., acute heart failure.

In the laboratory each afternoon I supervised five or six groups of four students each, and each group had a cat to anesthetize and experiment upon. And in learning the importance of uniform anesthesia and how to administer it, those students afforded me opportunities to see a far larger number of deaths under anesthesia than (I am sure) any of my many friends among professional anesthetists have ever caused or witnessed.

My own record also included several such catastrophes; one in particular was, at the time, a bitter disappointment. I learned its lesson later. A fine strong dog of irritable temper had been given me by a friend for an experiment on the circulation. I attempted to bring the dog under ether. He fought, breathed violently, came part way under the influence of the anesthetic, and then out again. Finally I succeeded in getting him quiet, and immediately he stopped breathing. My utmost efforts failed to induce him to breathe again. This was before I knew that an animal can breathe too much. Nothing whatever had been done to this animal, except to induce overbreathing by ether excitement, and then to induce apnea by restoring the threshold of the respiratory center to its normal level by full anesthesia; and before the apnea ended, asphyxia caused death.

While I was making such observations on animals there came to my attention the case of a man whose hand was injured by the explosion of a giant firecracker. After two hours of intense suffering he was etherized. He stopped breathing. And although his heart continued to beat for a few minutes, respiration was not restored.

I described and analyzed that case 25 years ago; yet such cases still occur. Only yesterday a little girl two years old caught her hand in a washing machine. Taken to the accident room of the hospital this scared and suffering child was anesthetized and passed into a fatal apnea. Then the interne found that although the hand was badly bruised, no bones were broken. (The excuse of course is "status lymphaticus" or some other fault of the patient; the interne responsible had never killed a cat).

From such experiences and observations on the students and on the cats, I was led gradually to a clear conception as to the cause of "respiratory failure under anesthesia"; and—no less important—to discover what an unskillful anesthetist does to produce such a catastrophe. It was a catastrophe that until recent years was sufficiently often fatal to be one of the dreads of every surgical operating room. At best the operation had to be suspended until the patient's breathing was restored, while the surgeon fumed and the anesthetist sweated with anxiety: neither knowing what was really wrong. Since the causation has been explained, it has become extremely rare. It was clearly a form of apnea vera augmented by anoxia: acapnia and anoxia, anoxia and acapnia.

To confirm this conception I began to do blood gas analyses with the mercury pump of Leonard Hill, the immediate precursor of the Van Slyke apparatus, and later with the Haldane ferricyanide and lactic acid method. These experiments, con-

ducted on dogs, demonstrated that the activity of respiration, as expressed by the volume of the pulmonary ventilation (the number of liters and cubic centimeters of air inhaled and exhaled in a minute) is not the result of one cause or factor. It is always the product of at least two main factors: two factors that are most conveniently denominated as (1) the strength of the stimulus, and (2) the sensitivity, or excitability, of the respiratory center.

This conception requires that carbon dioxide shall always be regarded as the sole chemical stimulus to respiration, either directly or through pH. All the other substances and conditions that increase or decrease breathing are denied as stimuli. They must rather be regarded as acting entirely by altering—either raising or lowering—the sensitivity of the respiratory center to carbon dioxide. Under this conception they are held to be stimulants, not stimuli. It is a conception that is indeed artificial and arbitrary, but extremely useful as a method of calculating results in a wide range of respiratory problems. It permits a very simple formulation of the interaction upon the respiratory center of carbon dioxide, with pain, fear, rage, or other mental excitement, as well as with morphine, ether in low and high concentrations, and slight and extreme oxygen deficiency. Thus, for example, under the influence of pain or other nervous or mental excitement the sensitivity of the respiratory center is so much increased that marked overbreathing occurs and a considerable degree of simple acapnia may result.

Morphine on the contrary decreases the sensitivity of the center. This in fact is its principal pharmacological action; respiration is then no longer induced by the normal amount of carbon dioxide in the lungs and blood, but decreases until a sufficiently increased amount of this chemical stimulus has ac-

cumulated to balance the diminished sensitivity of the respiratory center, and to maintain then a lessened volume of breathing. In extreme morphinism the concentration of carbon dioxide required to maintain any respiration at all is so high, and the pulmonary ventilation therefore becomes so small, that death from anoxia may result. In lesser amounts morphine, by largely diminishing the sensitivity of the respiratory center, is par excellence the antidote to pain and fear.

Ether, on the contrary, in amounts short of full anesthesia, increases, but in deep anesthesia decreases, the sensitivity of the respiratory center. An unmorphinized, excited, partially etherized patient or animal may overbreathe to such an extent that, when full anesthesia is induced, and the respiratory center is restored to normal or subnormal sensitivity, the amount of carbon dioxide remaining in the blood is insufficient to maintain respiration. Apnea then occurs, even though the patient or animal may not be profoundly anesthetized. In other words, the observations on student anesthetists with cats and my own follow-up experiments on dogs, showed that failure of respiration under anesthesia is not always, or mainly, due to excess of anesthetic, although an excess of anesthetic also tends to cause apnea. The failure is largely due to the acapnia previously induced.

In this sequence and interaction of conditions oxygen deficiency, either slight or considerable, also plays a major part. Slight anoxia acts as a stimulant to respiration: it increases the sensitivity to carbon dioxide long after the anoxia itself is relieved. It thus induces overbreathing and an increase of acapnia. Deeper anoxia, if prolonged, diminishes the sensitivity of the respiratory center to such an extent that far more than the normal amount of carbon dioxide is required to induce breathing. If on this account respiration is diminished or ceases, the anoxia increases; and death results.

INHALATION OF OXYGEN AND CARBON DIOXIDE

With these observations and ideas in mind I gladly accepted an invitation to address the Johns Hopkins Hospital Medical Society on December 6, 1909. My topic was "Fatal Apnea and the Shock Problem." I pointed out the importance of rapid induction of anesthesia, avoidance of anxiety and excitement, use of preliminary morphine (then rare), and prevention of over-ventilation by means of rebreathing. In concluding I reported that I had tried a new method of resuscitation "upon dogs during apnea with strikingly successful results. It consists in administering air or oxygen containing 5 or 6 per cent of CO₂ and starting the subject to breathing by one or two artificial respirations. As soon as the normal tension of CO₂ in the lungs is thus restored, spontaneous breathing immediately recommences and is maintained as long as the inspired air contains a sufficient quantity of CO₂ to stimulate the respiratory center. It will, I think, be advisable to use for this purpose oxygen and CO₂ and not merely air plus CO₂ for the purpose of eliminating (anoxial) acidosis.—It would be better to have the gases already mixed. I hope to be able to persuade the manufacturers to supply tanks of oxygen containing 5 or 6 per cent of CO₂ and I hope to be able to persuade clinicians to use it."

It all sounds so simple now, 28 years later, with mixtures of oxygen and carbon dioxide available everywhere, and anesthetists so well trained in the physiology of respiration that the most skillful rarely have to use this means of resuscitation. Yet it drew down upon me so devastating a criticism from the eminent professor of physiology of that very eminent place that, when given the floor for rebuttal, I could only smile and say: "I will see him outside"; although actually we were then, and have always been since, the best of friends. And as I look back, I

remember that there was another speaker, Dr. F. F. Russell of the United States Army, to whom I was to owe a great debt ten years later and who that evening made the first public report of the complete success of immunizing inoculations against typhoid fever. It was, I believe, rather a good evening even for the Johns Hopkins in its greatest days.

One other incident of that evening I must mention. Sitting in the front row was one of the oldest members of the faculty—a great surgeon and noble man—who on that and other occasions gave me the quiet words of encouragement that mean so much to a struggling young investigator. It was Dr. William S. Halstead.

Chapter III

THE FALLACY OF ASPHYXIAL ACIDOSIS

FAR greater difficulties lay ahead. By 1916 the development of the modern conception of acidosis seemed to afford decisive reasons for complete rejection of the method of resuscitation that I was trying to introduce. Its underlying ideas appeared to be utterly wrong. Inhalation of carbon dioxide should be, not helpful, but extremely harmful.

Ever since modern chemistry had begun to be applied to the problems of disease, analyses of the blood and urine had afforded an increasing mass of facts that were interpreted as indicating that the body may be poisoned by acids produced within its own tissues. It was supposed that the production of acids and their diffusion into the blood were among the most easily induced of all abnormal processes, and that the resulting condition of acid intoxication was as common as fever.

ACIDOSIS, OLD STYLE

In some conditions the acids were derived from fats. This occurred in diabetes, in which disease the tissues were unable to burn sugar, and the patients starved, while large amounts of sugar (glucose) were drained off in the urine. It was found that when this loss becomes so nearly complete that the tissues oxidize "more than three molecules of higher fatty acid to one of glucose, then the body 'smokes' with acidosis compounds like an automobile with too much oil in the cylinders," as Woodyatt picturesquely expressed it.

Back in 1883 Stadelmann, and a year later Minkowski, had found that in diabetes, particularly as coma developed and

death approached, large amounts of oxybutyric and other fatty acids appeared in the urine in combination with ammonia. In that observation the conception of acid intoxication originated. Without the formation of ammonia the acids would soon have carried out with them into the urine the body's entire store of sodium, potassium, and other alkalis. The capacity of the body to neutralize the acids with ammonia, which Benedict later showed to be produced in the kidneys, appears to be the last line of defense of the body against an overwhelming acidotic intoxication.

The conception of intoxication by acids was extremely attractive to clinicians in many fields. All agreed when Howland said that "acidosis in infancy and childhood is a frequent condition and an important one." The condition called "acidosis" in children was commonly an accompaniment of febrile disease. Acetone and related substances appeared in the urine, and could be smelled in the breath. Vomiting was common. The carbon dioxide content and capacity of the blood were diminished and there was overbreathing. When "acidosis" occurred with diarrhea, the child generally died.

In some forms of nephritis with edema, "acidosis" was also found. The diseased kidneys were unable to excrete sodium chloride sufficiently to keep this constituent of the blood down to its normal amount; and, in the effort to regulate the osmotic pressure of the blood, it appeared that sodium and other bases were excreted in excess. Consequently the phosphoric and sulphuric acids produced by protein metabolism were inadequately neutralized. Along with the resulting decrease of alkali in the blood, shortness of breath increased up to marked hyperpnea.

Even more important in their effects on current opinion were observations on carbon monoxide asphyxia and on the chemical

process involved in the contraction of muscles. Araki in 1894, working in Schmiedeberg's laboratory, had found that in animals, that had been partially asphyxiated with carbon monoxide and kept for a time in that state of subnormal oxygen supply to the tissues, considerable amounts of lactic acid appeared in the urine.

Even earlier, in 1877, Walter, also in Schmiedeberg's laboratory, had found that, when hydrochloric acid was administered to animals by stomach, the bicarbonates of the blood were decreased and respiration was increased. He first recognized that "the amount of carbon dioxide in the blood is proportional to the amount of alkali that the blood contains." These observations of Araki and Walter were together the basis for the universal belief, which has lasted down to the present time, that deficiency of oxygen prevents the oxidation of glucose and liberates lactic acid into the blood; and that the lactic acid then neutralizes a part of the alkali in the blood. Hence the conception of "asphyxial acidosis."

Equally confident was, and still is, the belief in the occurrence of a lactic acid acidosis of mild degree as the result of vigorous muscular exercise. Fletcher and Hopkins in 1907, showed that when frog's muscles were stimulated to work until fatigued in an atmosphere of nitrogen, glycogen disappeared and an equivalent amount of lactic acid was formed. And the line of thought thus initiated was developed later by the investigations of Meyerhof. They seemed to show that in the working muscle the molecule of sugar ($C_6H_{12}O_6$) first splits into twice as many molecules of lactic acid; and that this reaction is followed, during the relaxation and rest of the muscle, by the oxidation of part of the lactic acid and the resynthesis of the remainder back to sugar.

In the urine of men after violent exercise Ryffel had found lactic acid. Following this line A. V. Hill thought that in men dur-

ing a short period of vigorous exercise—such as a sprint—a marked excess of lactic acid must be produced and must involve what he termed an “oxygen debt.” The expenditure of energy was certainly much greater than would correspond to the amount of oxygen that respiration and the circulation could supply immediately to the working muscles. Lactic acid must accumulate; and this debt, he thought, was made good after the exercise ended by the large amount of oxygen then absorbed and utilized for the combustion of the accumulated lactic acid. The Hill-Meyerhof theory regarding lactic acid formation and combustion in muscular exertion seemed for a time so important, and was so much in accord with all that was then known, that its authors were accorded the Nobel Prize.

At that time no conception in the whole range of physiology appeared more certain than that, if to any degree the supply of oxygen falls short of the demand, lactic acid must accumulate in the blood and induce a corresponding degree of acidosis.

ACIDOSIS, NEW STYLE

Toward the end of the last century the great Swedish chemist Arrhenius developed a conception of the nature of solutions of far reaching application and importance. He showed that salts, acids and alkalis, when dissolved, are separated to a greater or less degree into their component elements, which then act as ions. To a small extent even pure water also separates into ions; and when the concentrations of H ions and OH ions are equal, the water or solution is neutral, neither acid nor alkaline. The presence of an acid such as HCl increases the H ions and correspondingly decreases the OH ions; and various acids have this effect according to the degree to which each is dissociated into its ions. Strong acids, such as HCl, are much dissociated;

weak acids like carbonic acid (H_2CO_3), are only slightly dissociated; and the concentrations of H ions that each induces vary correspondingly. The presence of an alkali, such as NaOH, or even $NaHCO_3$, has the opposite effect; it increases the OH ions and decreases the H ions. The acidity or alkalinity of a solution is therefore conceived as determined by the concentration of H ions: a quantity expressed by the symbol pH, the negative logarithm of their concentration.

This conception was introduced into physiology by L. J. Henderson, who showed that in the acid base balance of the blood the acid is chiefly carbonic acid (H_2CO_3), which is carbon dioxide in solution, while the alkaline factor is chiefly bicarbonates: $NaHCO_3$ in the blood plasma, $KHCO_3$ in the corpuscles, or $BHCO_3$ for both. Van Slyke recognized that to measure the bicarbonates, which he called the "alkaline reserve," it was necessary merely to determine the amount of carbon dioxide that could be obtained from the blood. For their measurement he invented the modification of the mercury pump that is now in universal use. Under this conception the alkaline reserve serves to neutralize any acid that may enter the blood, and thus normally protects the body from acidosis. If the "alkaline reserve" is lowered—that is, if the blood holds, or can hold, less than the normal amount of carbon dioxide—that condition is "acidosis."

Few developments in medical science have excited wider interest or met with more complete acceptance than the conception of "acidosis" thus defined. Accordingly it was made the subject of a general discussion before the Association of American Physicians in 1916. Eminent clinicians first presented papers dealing with the various conditions which they called "acidosis": papers from which I have quoted freely in the preceding section

of this chapter. Then two biochemists—L. J. Henderson and D. D. Van Slyke—presented their new conception of acidosis, essentially as it is summarized in this section. Everyone was delighted that Chemistry had come to the aid of Medicine and had solved this fundamental problem.

I was the last speaker on the program and ventured to point out that perhaps a number of different conditions were being confused under the same name. “Acidosis” in the biochemical sense could not be in itself the critical feature of the various conditions in disease that the clinicians called by that name. I had been a member of a party with Haldane, not a great while before, that had spent five weeks on top of Pike’s Peak. In all our bloods the alkali had there been reduced to levels that would indicate marked degrees of acidosis. Yet we all felt extremely well.

The protest was without effect: I had no adequate alternative to offer. And certainly nothing could be clearer or more logical and consistent with its premises than the conception of “acidosis” as there presented. And ever since then it has been taught to every medical student as necessarily true, because derived from a consideration of the blood as a physico-chemical system.

Doubt arises only when that conception is put to the crucial test, and proves in certain features to be flatly contradicted by observations on living men and animals.

ACIDOSIS AS EXCESS OF CARBON DIOXIDE

The foundation of the present conception of the acid base balance of the blood and of the disturbance of this balance in acidosis is the equation formulated by L. J. Henderson:

$$\frac{[\text{H}_2\text{CO}_3]}{[\text{BHCO}_3]} \times K = [\text{H}]$$

This equation is one of the most important contributions ever made to physiology and biochemistry. But it is often misinterpreted. In it $[H]$ expresses the hydrogen ion concentration of the blood; K is a constant; $BHCO_3$ is the "alkaline reserve"; and H_2CO_3 is the amount of carbon dioxide in the form of carbonic acid in simple solution in the blood. It is this last factor that particularly requires attention here.

Carbonic acid is a very weak acid: the weakest acid that we have seriously to consider in the body. For this reason it is the only acid that can exist free in the blood; for if any stronger acid, such as hydrochloric or lactic, enters the blood, it is immediately neutralized by base from the bicarbonates and a corresponding amount of carbonic acid is set free. The denominator of the expression $\frac{[H_2CO_3]}{[BHCO_3]}$ is thereby decreased, while the numerator is

increased and the H ions also. The essential feature of acidosis is then a relative excess of carbonic acid. And the lower the alkaline reserve, the less the amount of carbonic acid that will swing the acid base balance of the blood in the acid direction.

The blood is normally slightly alkaline (pH 7.35). If the bicarbonates are decreased and the carbonic acid is not decreased proportionally, the H ions are markedly increased. And because, in some conditions such as diabetes, coma and death occur when the alkalinity of the blood has decreased, and the H ions have increased beyond a certain degree (e.g. pH = 7.0), it is supposed that such a degree of "acidosis" is incompatible with life.

Such being the features of "acidosis" as now defined—low "alkaline reserve," relative excess of carbonic acid, increased lactic acid, and high H ion concentration—what could be more completely contrary to the clear meaning of biochemistry than

to increase the carbonic acid and H ions by administering an inhalation of carbon dioxide to patients already in a state of acidosis? No wonder the introduction of carbon dioxide as a means of resuscitation has met, at every step, with the most earnest protests from biochemists and clinicians too numerous to quote. They have demonstrated conclusively again and again that every one of the conditions to which carbon dioxide was applied—and applied with high success in the saving of life— involves a state of typical "acidosis."

Among those states was carbon monoxide asphyxia. The very foundation of the conception of asphyxial acidosis was Araki's demonstration of the production of lactic acid in this form of asphyxia. Oxygen is indeed generally mixed with carbon dioxide in the inhalation that now resuscitates thousands of the victims of carbon monoxide. But carbon dioxide mixed merely with air is almost as effective: much more effective than oxygen alone.

Closely related is the use of carbon dioxide in connection with anesthesia that has now become almost universal. Yet the findings of the numerous investigators who have examined the blood in patients and animals under anesthesia are summarized by Peters and Van Slyke as follows: "General anesthesia induced by ether and chloroform is attended by reduction of the bicarbonates of the blood and serum. Henderson and Haggard believed that the bicarbonate fall was a secondary effect of primary carbon dioxide deficiency brought about by over-ventilation during the excitement stage of anesthesia. It is now realized, however, that such a hypothesis is untenable. Van Slyke, Austin and Cullen, and Cullen, Kornblum and Robinson, have shown that both bicarbonate and pH fall early in the development of the acidosis, an indication that bicarbonate is displaced from combination with base by other acids."

Even more striking is the conflict of theory and practice in the asphyxia of the newborn in which the means of resuscitation now generally employed include carbon dioxide. Yet practically all the conditions of supposed acidosis have been found by Eastman in babies born in asphyxia: extremely low oxygen in the blood, with a high content of lactic acid, decreased alkali and high H ion concentration (low pH). And from these findings Eastman, in conformity with the conception of acidosis as acid intoxication, concludes that "the use of carbon dioxide as a resuscitating agent in asphyxia neonatorum is not only superfluous but may even be harmful in that it tends to aggravate an already existing acidosis." Eastman's analyses are verified by Noguchi.

Similarly Cannon, on the basis of his investigations during the War, warned against the use of carbon dioxide in postoperative depression and wound shock, because he found a low blood alkali in those conditions.

Even the lowered alkali, which is a constant feature of acclimatization in those who live at altitudes such as Denver, Cripple Creek and the towns of the Andes, is assumed to represent a chronic acidosis, although the inhabitants are quite healthy. On this assumption, an attempt is made to induce quickly an artificial acclimatization in those who, starting from sea level, are to fly over the Andes. For this purpose doses of ammonium chloride are administered: a chemical that liberates acid in the body and decreases the alkali of the blood. Whether or not a man's "ceiling" is thereby raised as Christensen and Smith claim, his condition is certainly very different from true acclimatization. His "ceiling" would better be raised by inhaling a little carbon dioxide: raised, perhaps, from 10,000 up to 15,000 feet, but not safely higher.

Equally doubtful have proved the benefits that, on the basis

of theory, should be expected from the administration of alkali to patients in a clinical "acidosis," so-called. Particularly in diabetic "acidosis," before the discovery of insulin, sufficient alkali was often administered to restore the normal bicarbonate content of the blood; yet the patients died. The significant fact is that even when a diabetic "acidosis" has reached the stage of coma and death impends, no great amount of alkali has been lost from the body. It has merely been displaced from the blood coincidentally with disturbance of sugar metabolism; and an artificial restoration of a normal blood alkali may even be harmful. Quite different is the influence of insulin, for with the restoration of the metabolism of sugar, a rapid return of alkali from the tissues to the blood occurs. Doubtless in any condition of true acid poisoning alkalis must be beneficial. Whenever they are not, that fact speaks against the condition being anything more than a displacement of alkali from the blood to the tissues. Such appears to be the case in the hyperglycemia and supposed "acidosis" of carbon monoxide asphyxia. So at least my experience would indicate; for I once administered a sodium bicarbonate solution intravenously to a man in carbon monoxide coma, and the effect fell just short of immediate death.

Those who still cling to a belief that oxygen deficiency induces, not merely a displacement of alkali from the blood, but an acid intoxication, can easily put their faith to the test. Let them take four puppies or kittens of a litter and asphyxiate them with city gas nearly to the point of death; then lay one aside as a control; treat a second with an intravenous injection of sodium bicarbonate; a third merely with oxygen; and a fourth deeply asphyxiated subject with an inhalation of 6 to 8 per cent of carbon dioxide in air.

ACARBIA

Jean Jacques Rousseau reported his Savoyard Vicar as saying: "To be in doubt, about things which it is important for us to know, is a situation too perplexing for the human mind; it cannot long support such incertitude but will, in spite of itself, determine one way or the other, rather deceiving itself than being content to believe nothing in the matter." Certainly, in respect to the conditions called "acidosis," belief based on a beautiful theory has prevailed, as against the incertitude that the facts alone warrant. If, however, we are to be less credulous and more scientific than the Vicar, it is essential, first, to stop applying the term "acidosis" to every condition of lowered blood alkali without distinction; and then to find a term that means low blood bicarbonates, but that is free from any implication as to how the lowering has been induced. Such a term is "acarbia." It means subnormal bicarbonate and nothing more.

Now there are, in fact, in addition to the clinical acarbias—some of which may perhaps be true acidosis—at least four ways of inducing acarbia experimentally; and perhaps others may yet be discovered. They are: by means of altitude, by means of acapnia, by means of asphyxia, and by administration of acids. Only the last of these forms of acarbia is certainly an acidosis. And it differs from the others in a crucial and easily demonstrated feature.

Altitude. The fundamental condition that determines the amount of alkali in the blood of all healthy men is the barometric pressure or, more exactly, the pressure of oxygen under which they live. That such is the case follows from Haldane's discovery of the lowering of the alveolar carbon dioxide with the barometer and from L. J. Henderson's equation. This relation of the blood alkali to the barometer was first shown in the ob-

servations of the expedition, in which Haldane, Douglas, Schneider, and I participated, that spent five weeks on Pike's Peak in the summer of 1911. It was confirmed both by FitzGerald's observations in towns at various altitudes in Colorado that summer, and by the expedition led by Barcroft to the Andes a few years later. It has been further supported by observations during a more recent expedition to the Andes and by the expeditions to Mount Everest in the Himalaya.

The facts are that as these expeditions mount to greater and greater altitudes, where the pressure of oxygen is lower and lower, each man slowly becomes acclimatized. As the primary feature of acclimatization, the breathing even during rest (measured in liters per minute and per gram of carbon dioxide) increases with each successive lowering of the barometric and oxygen pressure. The increased breathing dilutes the carbon dioxide in the lungs, and thereby decreases the carbonic acid in simple solution in the blood. It then tends also to draw carbon dioxide from the bicarbonates and to drive their alkali out of the plasma and into combination with hemoglobin in the corpuscles, or into the tissues and urine. Accordingly, when, after days or weeks, acclimatization is complete, it is found that respiration is increased, the alveolar carbon dioxide is lowered, and the blood is set at a degree of acarbia corresponding to the oxygen pressure in the air at that particular altitude. And this condition continues until the man returns to sea level or moves to some other altitude. For every altitude there is a quite definite degree of acarbia.

These facts demonstrate both that the fundamental factor controlling the blood alkali is the pressure of oxygen; and that the control is exerted through respiration. There is nothing in the voluminous literature of the physiology of mountaineering that indicates that any considerable production of acid within the body is involved. On the contrary, those who have par-

ticularly studied this matter (Haldane, Haggard, Henderson, Barcroft and Krogh), are in agreement that the first reaction to decreased oxygen is the increased breathing, which decreases the carbonic acid in simple solution in the blood, and leaves the blood slightly more alkaline than normal. The alkali then falls through some compensatory process, chiefly in the tissues, that keeps the concentration of H ions (pH) in the blood nearly the same as that which is normal at sea level. What this process in the tissues is, we do not know. But the volume of the tissues is so large in comparison to the volume of the blood that no considerable alteration in their acid base balance need be involved.

Acapnia. In the previous chapter are recounted my early observations on the effects of excessive ventilation of the lungs and the resulting acapnia. After Van Slyke's work appeared, I realized that any considerable degree of acapnia is impossible without acarbia also. A relatively small part of the carbon dioxide in the blood is in simple solution as carbonic acid (H_2CO_3). The greater part is held by alkali as bicarbonates.

Accordingly Haggard and I ran a series of experiments (1918) in which we demonstrated that by merely varying the ventilation of the lungs, and thereby adjusting the concentration of carbon dioxide in the blood, we could induce a marked decrease or increase in the amount of alkali in use. When the lungs of an animal were over-ventilated, and the carbon dioxide in the blood was thus decreased, the alkali also was greatly decreased. (For such ventilation a double pump that both inflates and deflates the lungs is essential.)

Contrariwise when respiration was depressed by means of morphine and the animal inhaled air containing five or six per cent of carbon dioxide, a very considerable increase of alkali

developed in the blood. As we expressed it, an increased pressure of carbon dioxide "calls alkali into the blood," although we were unable to define whether, in the exchange with the tissues, the alkali itself comes into the blood or chloride goes out. We concluded that instead of the blood alkali controlling respiration to the extent that is generally believed, respiration rather controls the blood alkali.

Cannon opposed the idea that this form of control can be of importance in clinical acarbias: such as wound shock. He claimed that no sufficient increase of breathing occurs. But in fact an increase of breathing to double the normal volume is scarcely observable. And when the volume of pulmonary ventilation is doubled and the H_2CO_3 in the blood thereby decreased by one half the blood alkali must also be decreased by one half, if a normal pH is to be attained: as L. J. Henderson's equation requires.

This at least is certain: any considerable degree of acapnia soon induces acarbia. No production of acid is involved. In states of depression less carbon dioxide is produced; and acapnia may develop without excessive breathing.

Asphyxia. A deprivation of oxygen of such extreme degree as soon to cause death induces a considerable production of lactic acid. On this ground it has long been assumed that a less marked deprivation must induce to some degree the same effect. Greenberg and I have shown, however, that this is not the case; and furthermore, that lactic acid plays little or no part in the increased respiration and other symptoms that occur as asphyxia develops.

Not long before our experiments were done (1934), Lundsgaard had shown (1930) that muscles that had been treated with monooiodoacetic acid were rendered incapable of producing lactic

acid. Yet they contracted quite normally. This important observation eliminated the principal foundation of the Hill-Meyerhof theory of muscular contraction. It goes far to eliminate both the idea that the oxygen debt of vigorous exercise is due to accumulation of lactic acid, and the belief that the decrease of the blood alkali after vigorous exercise is due to its neutralization by that acid.

Be that as it may, monoiodoacetic acid afforded Greenberg and me a means of determining what part, if any, lactic acid plays in the decrease of the blood alkali in asphyxia. We first determined the course of events in normal dogs that were subjected to progressive decrease of oxygen until death; and we then made the same observations on dogs that, by means of monoiodoacetic acid, had been rendered incapable of producing lactic acid. And the course of events proved to be exactly the same in the two groups, except that the uniodized animals survived to a slightly lower pressure of oxygen. So far as a lactic acid acidosis plays any part in the final stage of asphyxia, it tends to prolong life: an influence which inhalation of carbon dioxide reinforces.

Evidently then the acarbia induced by asphyxia is not an acidosis, even though the blood alkali is decreased and in the terminal stages, when respiration is depressed the H ions are increased (pH lowered) to an extreme degree. Furthermore the uniodized animals that, after being reduced to an extreme degree of asphyxia, were treated with 8 per cent carbon dioxide in air, recovered much more readily and rapidly than did a control group without the addition of carbon dioxide. The high concentration of carbon dioxide hastened the "recall of alkali to the blood."

The conclusion that an asphyxial acarbia, even of fatal degree, does not involve an acidosis has recently brought objections from

Thiel in Germany and Kamei and Hashimoto in Japan. They agree that inhalation of carbon dioxide is an effective means of resuscitation from carbon monoxide asphyxia. According to Thiel the beneficial effect is largely upon the circulation; and this, I also believe. In the last stage of asphyxia, however, they still insist that, as the alkali and pH are low and lactic acid high, there must be acidosis.

In reality the low pH merely means that after prolonged exposure to oxygen deficiency, respiration is depressed; carbon dioxide accumulates; the alkali is already low; and the ratio $H_2CO_3 : BHCO_3$ swings to the acid side. These investigators and many others overlook the influence of respiration on the pH of the blood. In blood the pH is never an inherent quality, as it is in a solution of HCl or NaOH. It is always imposed on the blood by the volume of breathing at the moment. A slightly excessive ventilation of the blood as it passes through the lungs—that is, excessive in relation to the alkali—induces a pH above normal. A slightly depressed ventilation induces a pH below normal. Respiration thus controls the pH of the blood as L. J. Henderson's equation requires. High and low pH do not indicate alkalosis or acidosis. They indicate only the activity of respiration in comparison with the amount of the alkali in use in the blood.

Administration of Acid. Many have administered acids and written about acidosis. It is somewhat surprising, therefore, to find from a review of the literature, that Haggard and I are the only investigators, since Walter's experiments 60 years ago, who seem ever to have induced and studied fatal degrees of acid intoxication. Hasselbalch originated the idea that the acid base balance of the body may be considerably influenced toward acidity by a meat diet and toward alkalinity by a vegetable diet.

But, as Nielsen shows, the data can be explained as well by alterations of the excitability of the respiratory center as by excess of acid or alkali. Given sufficient time the animal body can dispose of enormous amounts of acid with no disturbance of health whatever. Lamb and Evvard administered 200 to 300 cc. of normal sulphuric acid daily to swine through three generations, and equivalent amounts to three generations of rats. Rabbits tolerated 5 cc. of the same acid daily for long periods, but succumbed to larger amounts, as Walter previously had found. In Walter's dogs vomiting prevented the ingestion of fatal amounts of hydrochloric acid. Yet the amounts that were retained and absorbed were so large that, if the acid had reacted with the blood alone, the entire "alkaline reserve" would have been neutralized and replaced by acid: a condition wholly incompatible with life. Instead the animals survived; and their blood, as shown in a typical experiment, still contained enough alkali to hold 18 volumes per cent of carbon dioxide. The greater part of the acid was excreted in combination with ammonia.

In the experiments that Haggard and I carried out, normal hydrochloric acid was administered to dogs intravenously at uniform rates of 0.25 to 1.00 cc. per minute for one to three hours. The total amounts of acid were very large: sufficient in fact to neutralize twice or thrice the entire alkali bicarbonates of all the blood in the body. (See table I.) Yet even a couple of minutes after the injection was ended analysis showed that only a third to a half of the bicarbonates had been neutralized. Several of the animals died in acidotic convulsions; yet in a case that just failed to die, the blood alkali had returned to its original level in 24 hours; and the animal was entirely normal. Evidently the capacity of the animal body to resist acid intoxication

TABLE I

Showing that, when hydrochloric acid is injected intravenously in dogs in amounts and at rates sufficient to induce a fatal, or nearly fatal acidosis, and more than equivalent to the bicarbonates of the blood, the bicarbonates are actually decreased by less than one-half, often only by a third; that by far the greater part of the acid is therefore neutralized by alkali other than that of the blood bicarbonates; that the rate of injection is as important as the amount; and that, if the animal survives, the bicarbonates return to the blood quite rapidly through some active remedial process

The acid was injected in small, uniform, repeated doses up to the amounts of 22 to 55 millimoles per liter of blood in the animal. The blood volume was estimated as 70 cc. per kilo body weight.

The data are derived from Haggard and Henderson, *J. Biol. Chem.*, 1919, 39, 163.

NUM-BER OF EXPERIMENT	BICAR-BONATE BEFORE INJEC-TION	HCl IN-JECTED	BICAR-BONATE AFTER INJEC-TION	PER-CENT-AGE OF BICAR-BONATE NEU-TRAL-IZED	PER-CENT-AGE OF HCl NEU-TRAL-IZED BY BICAR-BONATE	DURA-TION OF INJEC-TION	NOTES
	mM. per liter of blood	mM. per liter of blood	mM. per liter of blood			minutes	
5	22.5	33	12.6	44	30	120	Survived
2	22.5	35	10.8	52	33	190	Survived
3	19.3	28	11.7	40	27	180	Survived
4	20.2	35	13.9	31	18	180	Survived
6	21.6	55	9.9	54	21	70	Survived
7	20.2	39	9.4	53	28	130	Survived
8	20.2	28	14.4	29	21	55	Restored with NaHCO ₃
10	20.2	25	12.2	40	32	60	Died in 5 minutes
11	18.9	27	10.6	45	31	38	Died in 3 minutes
12	20.7	22	8.1	61	57	40	Died in 2 minutes
13	18.4	29	15.7	15	9	105	Died under inhalation of CO ₂
14	20.2	42	11.7	42	20	180	Died under inhalation of CO ₂
15	19.8	27	14.4	27	20	75	Died under rebreathing
16	21.1	25	15.7	26	22	40	Died under rebreathing
17	21.6	38	8.5	54	31	70	Died after moderate dose of morphine

In experiments 2, 3, 4, 6 and 7, the bicarbonates at 2.5, 1.5, 1.0, 1.0 and 24 hours after the end of the injections had risen again to 13.9, 13.9, 15.2, 15.2 and 20.2.

is due only a small extent to the so-called "alkaline reserve" of the blood. Even in extreme cases of experimental acid intoxication the bicarbonates of the blood play only a minor part in its defense. Decrease of the bicarbonates in disease and asphyxia, on the contrary, is generally due to some cause other than neutralization by acid. That cause is commonly the acapnia resulting either from the overbreathing induced by oxygen deficiency or from the diminished production of carbon dioxide incident to states of depression. Even in plants, as Thornton reports, an increased pressure of carbon dioxide in the atmosphere induces an increase, not of acidity, but of alkalinity and of the bicarbonates in the tissue juices.

The outstanding feature of our experiments with acids was that these truly acidotic animals were quickly killed by an inhalation of 5 to 6 per cent of carbon dioxide. They reacted, in fact, exactly as Van Slyke, Cannon, Eastman, and many others claim that acarbia patients also should act; but in fact do not. In the effects of inhalation of carbon dioxide we have therefore a crucial test whether in any condition of acarbia the state is acidotic or not. If it is, carbon dioxide may kill. If it is not, it tends to cure.

EXPERIMENTS BY TWO HALDANES

It was always the custom of the late J. S. Haldane to do his experiments largely on himself. He subjected himself repeatedly to carbon monoxide asphyxia, to compressed air in a caisson, to altitudes and to low oxygen in a closed chamber or by rebreathing. He must often have developed a considerable acarbia, and have experienced the shortness of breath and panting on exertion that acarbia of any form always induces.

This practice was continued by his son, J. B. S. Haldane, who

subjected himself also to an acute acarbia but of a quite different type. He swallowed considerable amounts of ammonium chloride: equal to nearly a liter of a normal solution in three days. The ammonium was converted into urea, and the hydrochloric acid that remained then displaced a part of the carbon dioxide from the bicarbonates of the blood and diminished their amounts. And as his father told me, "I was almost ashamed to walk with him at a leisurely pace along the streets of Oxford, for he was panting so hard as to attract everyone's attention."

TABLE II

Comparing the conditions in the blood of J. S. Haldane at Oxford (Bar. 760 mm.) and after 5 weeks on Pike's Peak (Bar. 460 mm.) with those in J. B. S. Haldane before and after taking 55 grams of ammonium chloride in 3 days

The blood alkali of J. S. Haldane is estimated from his alveolar CO₂, assuming a normal pH, as other evidence indicates.

	J. S. HALDANE		J. B. S. HALDANE	
	Oxford	Pike's Peak	Normal	After NH ₄ Cl
Alveolar CO ₂ , mm. Hg.....	40.7	25.7	39.1	27.4
Alkaline reserve, vols. per cent at 40 mm. Hg.....	50	31	48.1	28.2

The conditions in the blood of these two men were much the same. But the conditions in their bodies were fundamentally different. One had lost no considerable amount of alkali from his tissues. The other had taken into his body 20 times as much HCl (in the form of NH₄Cl) as any of the dogs reported in Table I; but he had wisely taken it over three days, instead of three hours. One acarbia was of the barometric, asphyxial, or acapnial type. The other was of the acidotic type. An inhalation of carbon dioxide for one of these subjects would have hastened the recall of alkali to his blood and aided his restoration to normal

physiological condition. The same inhalation, if pushed at all, would probably have killed the other. That is the practical difference between a non-acidotic acarbia and a true acidosis.

THE RESERVE OF ALKALI

The misconception with which this chapter deals arises largely from the use of the expression "alkaline reserve," introduced by Van Slyke, to indicate the bicarbonates of the blood. In reality the bicarbonates, as Van Slyke himself has shown, constitute only a small part of the alkali of the blood. They are not its reserve. They represent only the alkali in use for the transportation of carbon dioxide. The true reserve of alkali is held in combination with hemoglobin. According to measurements that Greenberg and I have made recently, 80 per cent of the total alkali of normal blood is held by hemoglobin, BHb, and only 20 per cent is in the bicarbonates, as BHCO_3 . Further observations on animals (as yet unpublished) indicate also that in a true acidosis, as in J. B. S. Haldane, the alkali held by hemoglobin is considerably decreased, while in such an acarbia as that of J. S. Haldane this fraction of the blood alkali may even be increased. Yet their bicarbonates were decreased about equally.

Chapter IV

THE CONTROL OF BREATHING AND BLOOD ALKALI

IN ALL conditions in which the blood alkali is low, the subject, man or animal, is more or less short of breath. He may feel as if he cannot get enough air. Actually in most cases he breathes, not a smaller, but a larger volume of air than does a normal man or animal. This hyperpnea is particularly marked under any considerable muscular exertion. He may be short of oxygen, but often he is not. On the contrary, a low content of bicarbonate in the blood is frequently associated with panting and the sensation that accompanies it. The obvious implication of this fact is that acidification, or at least diminished alkalinity, of the blood, by increasing the H ion concentration, is the cause of the increased breathing. In addition we have only to assume, as many still do, that a deficiency of oxygen induces acidosis; and the conception is then coherent and complete.

The only defect is that deficiency of oxygen does not induce acidosis.

In the previous chapter we saw that J. B. S. Haldane, after decreasing the bicarbonates of his blood with hydrochloric acid from the ammonium chloride that he had swallowed, was easily out of breath. We saw also that J. S. Haldane, during his stay on Pike's Peak, developed a condition superficially similar, but fundamentally different. In this chapter it will be shown that, while in J. B. S. Haldane the low alkali increased breathing, in J. S. Haldane it was the increased breathing that lowered the alkali. And if this is true, it leads us to the conclusion that in the type of acarbia that is induced by anoxia, the alkali of the

blood, instead of being a major influence upon respiration, is rather itself controlled by respiration.

ENERGY EXPENDITURE AND LUNG VENTILATION

The control of breathing has been the subject of a vast amount of investigation. It involves many factors: oxygen, carbon dioxide, blood alkali and H ions, and particularly the sensitivity of the respiratory center under a wide range of conditions and influences. For conditions of health the accepted teaching is that of Haldane and his collaborators. It can be summarized in the statement that a normal man, engaging only in moderate physical activities, breathes, when at rest and during and after those activities, volumes of air that are closely proportional to the amounts of carbon dioxide that are produced in his tissues. When he sits still, the amount of energy liberated in his body and the amount of carbon dioxide produced are relatively small; and he breathes a correspondingly small volume of air. When he walks about and produces more carbon dioxide, he breathes more air in proportion to the carbon dioxide. In other words, he ventilates his lungs in close proportion to the energy expended and the oxygen needed; but the agent through which the adjustment is made is carbon dioxide.

THE INTERIOR ATMOSPHERE

The blood that flows out of each organ into the veins is in gaseous equilibrium with the tissues through which it has passed. The blood from all parts of the body unites and mixes in the large veins, and then flows through the lungs, where it comes into virtually complete gaseous equilibrium with the air in the pulmonary saccules and alveoli. But this interior atmosphere—the so-called alveolar air of the lungs—has a very different com-

position from that of the outside air. The air outside the body contains almost 21 per cent of oxygen and only a few hundredths of one per cent of carbon dioxide. The air in the lungs of a normal man at sea level (Barometer 760 mm.) is regulated by respiration to contain about 5.5 per cent (42 mm.) of carbon dioxide, beside a considerable amount of water vapor (50 mm.) and therefore only about 13 or 14 per cent of oxygen.

From the lungs the blood is pumped into the arteries by the heart and distributed in varying amounts to all parts of the body: a large supply to some organs, a relatively small supply to others. And of all the organs the supply to the brain is probably the largest in proportion to its metabolism. Consequently the tensions of the various gases dissolved in the fluids and tissues of the brain are kept very nearly the same as those in the arterial blood, and thus in turn the same as in the lungs. This uniformity as between the lungs, arterial blood and brain, is true not only in regard to the tensions of oxygen, nitrogen and carbon dioxide; it is true also for any foreign gas. When such a gas as nitrous oxide, or the vapor of ethyl ether, is drawn into the lungs, the blood flowing through the lungs immediately comes into gaseous equilibrium with it and carries it to the brain; and within a few seconds the tension (partial pressure) of that gas in the brain becomes the same as that in the blood and lungs. It is because of this relation of the lungs, blood and brain that the volatile anesthetics administered through the lungs act so much more rapidly than drugs administered through the stomach, or subcutaneously: more rapidly even than those injected intravenously.

The lungs are nearly perfect organs for the almost instantaneous diffusion of gases between the air within them and the blood flowing through them. The flow of blood from the lungs to the

brain requires but a moment. And in the base of the brain is placed the respiratory center upon which any alteration in the carbon dioxide content of the blood acts almost instantly to increase or decrease the ventilation of the lungs, and in this way to regulate and maintain nearly uniform the interior atmosphere of the body.

Such is the mechanism revealed by the celebrated "crossed circulation" experiment of Leon Fredericq in which he attached an artery of dog A to the head of dog B, so that the brain of B was supplied with blood that had passed, not through its own lungs, but through the lungs of dog A. And he found that B breathed more deeply when carbon dioxide was administered, not to its own lungs, but to the lungs of A.

THE RESPIRATORY CENTER

The respiratory center continually discharges a rhythmic succession of nervous impulses through the motor centers in the spinal cord to the diaphragm and the muscles of the chest; and the rate and strength of these impulses determine the frequency and volume of the breaths. In order that the interior atmosphere shall be kept nearly uniform—as it is even under wide variations of bodily activity, so long as the barometric, or oxygen, pressure is not considerably changed—it is essential that the ventilation of the lungs each minute shall be accurately adjusted both to the amount of carbon dioxide produced in the body and to the tension of oxygen in the arterial blood. To attain these objects the activity of the respiratory center is determined by two main conditions. One of these conditions is the amount of the stimulus, which is applied through carbon dioxide. The other condition is equally, or even more, important: it is the excitability of the center under that stimulus.

And the excitability is largely determined by the tension of oxygen; or, more precisely, by the relation between the tension of oxygen and the amount of alkali in use in the blood.

The relation of these two influences to each other in respiration may be illustrated by comparing the regulation of the interior atmosphere of the body to the regulation of the temperature of the air in a house with central heating controlled by a thermostat. In mild weather the thermostat induces only a small activity in the furnace. In cold weather the slight cooling of the house acts as a stimulus to the thermostat, which then increases the activity of the furnace. Similarly the production of a small amount of carbon dioxide, as during bodily rest, induces only gentle breathing; but the production of a large amount of carbon dioxide during muscular activity induces a correspondingly greater activity in respiration.

The analogy can be carried further. On every thermostat there is an adjusting dial by which the instrument may be set to maintain any desired temperature in the house: 60°, 65°, 70°, or even 80°. And it is this feature of thermostatic control that furnishes an enlightening analogy to the excitability of the respiratory center. It is the excitability of the center that determines whether respiration shall maintain the air in the lungs at 6 per cent (45 mm.) of carbon dioxide, or 5, or 4 (30 mm.), or even at some lower tension, as it does in healthy people acclimatized to altitudes many thousands of feet above sea level. And the factor which is mainly effective in adjusting and setting the excitability of the respiratory center to carbon dioxide is the tension of oxygen in the atmosphere, which is always close to 21 per cent of the barometric pressure at the locality where the people so adjusted live.

The distinction between stimulus and excitability is not merely

theoretical; it is extremely practical. Suppose that a man sitting still at sea level produces 250 cc. of carbon dioxide per minute and ventilates his lungs so that the air within them contains 5 per cent (38 mm.) of carbon dioxide. He will then breathe $250 \times \frac{100}{5} = 5,000$ cc. of air. Suppose now that he walks about at a fair pace and produces 500 cc. of carbon dioxide and ventilates his lungs so that the air within them still contains 5 per cent of carbon dioxide. He will now breathe $500 \times \frac{100}{5} = 10,000$ cc. of air. Suppose now that he were to go to live at a great altitude and to become so completely acclimatized to the lower tension of oxygen that his respiration automatically maintains the carbon dioxide in his lungs at only 2.5 per cent of a sea level atmosphere (19 mm.). As he still produces the same amount of carbon dioxide as at sea level he will then breathe $250 \times \frac{100}{2.5} = 10,000$ cc. of air even when he is sitting still. The first of these two adjustments involves a change in the amount of the stimulus without change of excitability. The second involves a change in the degree of excitability without change in amount of stimulus. Stimulus and excitability are thus independent variables. It is only in the over-breathing, rising to dyspnea (heavy panting), in a man who has made so vigorous an exertion that his muscles for a time are affected by oxygen want, that stimulus and excitability are both increased.

THE TIME THAT THE BREATH CAN BE HELD

The distinction between stimulation by carbon dioxide and the increase of excitability induced by a lower tension of oxygen can be easily demonstrated by any one, even without ascending a mountain, or making a vigorous muscular exertion. He need only determine how long he can hold his breath under conditions

that are varied in respect to carbon dioxide and oxygen, as in the five following experiments:

- (1) A normal man at sea level usually finds that he can voluntarily stop breathing for 40 to 60 seconds.
- (2) If he merely fills his lungs with pure oxygen before hand, he is in most cases unable to hold his breath any longer than before, or at most only a few seconds longer.
- (3) If, without using oxygen, he first performs forced breathing, so as to over-ventilate his lungs and blood, he can hold his breath for much longer, even up to two or three minutes.
- (4) If, however, he does the forced breathing with a rubber or paper bag held over his nose and mouth, he can then hold his breath for no longer than in the first experiment, or perhaps not even so long.
- (5) If, finally, at the end of several minutes of forced breathing, he fills his lungs with pure oxygen, he will be able to go for 5 or 6 minutes, or even 10 minutes or more, before the breaking point is reached and he is forced to breathe again.

The explanation of these results is that in the first and second experiments it is the accumulation of carbon dioxide that ends the apnea; for no appreciable shortage of oxygen develops in only one minute, even in the first experiment, and certainly none in the second.

In the third experiment the apnea is prolonged because part of the carbon dioxide has been ventilated out of the blood; and it takes some time to reaccumulate. But no over-oxygenation is involved; for the blood can take up no excess of oxygen under forced breathing of mere air. The apnea is ended by the combined effect of the reaccumulated carbon dioxide and the increased excitability of the respiratory center under the shortage of oxygen that develops during the prolonged respiratory standstill.

In the fourth experiment the bag prevents over-ventilation; and, if held tight on the face, it may cause such an accumulation of carbon dioxide that the apnea may be shorter than in the first experiment.

In the fifth experiment the inhalation of oxygen delays the anoxial increase of excitability that occurred in the third experiment, and thereby lengthens the time before the stimulus and excitability act together to force the return of breathing.

If the alveolar air is analyzed at the "breaking point" in each of these experiments it is found to contain less carbon dioxide in the third and fifth experiments than in the other three. This indicates that under anoxia the respiratory center is more readily excited. In other words, a lower pressure of carbon dioxide is sufficient to force a return of breathing.

THE EXCITABILITY OF THE RESPIRATORY CENTER

The conception that the volume of the ventilation of the lungs is not merely the result of the amount of stimulus, but is rather the resultant of stimulus and excitability, was first clearly stated by Cohnstein and Zuntz 50 years ago (1888) in a paper that is one of the classics of physiology. They were investigating the apnea of the fetus in utero and the beginning of respiration at birth, and were attempting to determine the causes of the change from one condition to the other. They concluded that in the newborn, as in the adult, the activity of breathing is the resultant of two factors: stimulus and excitability. They recognized that, while the stimulus is mainly carbon dioxide, the excitability of the respiratory center to that stimulus is increased by a slight degree of oxygen want, but is depressed by acute oxygen want. And they concluded that with the increase of metabolism that occurs at birth both factors are augmented. They would, I

think, have concurred in the view that, when the excitability is depressed, a stronger stimulus is required to induce breathing.

These conceptions were supplemented by Geppert and Zuntz in a paper in the same volume of Pflüger's Archiv on the regulation of respiration, particularly in relation to muscular activity. They showed that, when muscles do vigorous work, they not only consume oxygen and produce carbon dioxide; but that they also liberate some non-gaseous substance which is carried by the blood to the brain and there, directly or indirectly, increases the excitability of the respiratory center. For this substance many years later (1920) I suggested the name "respiratory X"; but as the "X" suggests something mysterious, it is better to call it "hyperpnein." In Geppert and Zuntz' experiments the spinal cord of an animal was cut at the level of the ninth rib, so that no nervous impulses either painful or stimulative could pass upward. Then by electrical stimulation of the spinal cord below the cut, the muscles of the hind legs were made to contract vigorously. They were, in fact, overworked; and, under the influence of the blood from the overworked muscles, the animal over-breathed. In other words, while the production of carbon dioxide was considerably increased, the breathing was increased still more. The lungs were over-ventilated; and the amount of carbon dioxide in each cubic centimeter of arterial blood, instead of being increased, was actually decreased. The hyperpnea was exactly like that which occurs in a normal man whenever he exerts his muscles up to some degree of oxygen want. Loewy pointed out that the hyperpneic substance is easily oxidized.

In other papers from Zuntz' laboratory Lehmann suggested that "der räthselhafte Stoff" might be lactic acid. And in fact, lactic acid is produced in overworked muscles and passes into the blood where it releases a small amount of carbon dioxide

from the bicarbonates. But the amount of carbon dioxide that can be thus released is only one-third of the amount that would result from the combustion of the lactic acid ($C_3H_6O_3$); and the extent to which the bicarbonates are decreased, even under the greatest production of lactic acid that ever occurs, is quite insufficient to account for the hyperpnea of vigorous exercise. Hyperpnein, whatever it is, is not an acid.

Alike untenable is the idea that lactic acid causes the increase of respiration under deprivation of oxygen and during the development of asphyxia. For, as Greenberg and I have found, there is no increase of lactic acid in the stages of asphyxia in which respiration is increased. Lactic acid appears in the blood in large amounts only in the final stage of asphyxia, in which respiration is depressed. Yet the idea that lactic acid must be a respiratory stimulant still persists. And, failing to find an increase of lactic acid or other alteration in the blood, sufficient to excite respiration, Gesell has argued that low oxygen must induce a formation of lactic acid in the respiratory center itself. The idea is based on the old belief in "asphyxial acidosis." It assumes also that the excitability of the respiratory center is unvarying; and that oxygen want acts upon respiration in the same manner as carbon dioxide.

Conclusive evidence against this conception of an "acidosis" localized in the respiratory center has now been afforded by the observations of Heymans, Bouckaert, Regniers, Cordier and Dautrebande. These Belgian investigators have demonstrated in brilliant fashion that oxygen want acts upon respiration in a wholly different manner from carbon dioxide. While carbon dioxide acts mainly upon the center itself, a slight want of oxygen exerts its stimulating influence through nerve endings in the sinus caroticus, a bulb at the bifurcation of the carotid

artery under the angle of the jaw. The tension of oxygen must be reduced to the point of acute asphyxia before the respiratory center itself is directly affected; and then it is not stimulated, but paralyzed. Such evidence proves conclusively that oxygen want does not act through the same means as carbon dioxide, since it does not act at the same place.

What hyperpnein, the "mysterious substance," really is, we do not yet exactly know. We know only that it is produced in the muscles, and perhaps in other tissues, under intense exertion or oxygen want, and that it probably acts, not directly upon the respiratory center, but through the nerve endings in the sinus caroticus. The choice is wide; for there are many substances that, when introduced into the blood, induce over-breathing and, as the Germans express it, an "Auspumpung" of carbon dioxide. Among the substances that are strongly hyperpneic, even in extremely small amounts, are sulphides, cyanides, iodoacetic acid; and among the less hyperpneic, ethyl ether, acetone and many tissue extracts. The chemical task is to isolate and identify the particular substance, or substances, from the blood after vigorous exercise or in the early stages of asphyxia.

What we have to explain is not why a man breathes more air during and after moderate exercise. The problem is rather why, when he makes a greater exertion, he is "out of breath"; in other words, he over-breathes. The challenging facts are that by over-breathing he lowers the carbon dioxide in his arterial blood, and temporarily renders his blood more alkaline (higher pH); and that he does so only during and after such an exertion that his muscles are affected by some degree of oxygen want.

Most extraordinary is the fact that what is here spoken of as "oxygen want" is merely exposure to a diminished tension of oxygen in the air or in the tissues. It is not a real deficit. This

is shown most clearly in the fact that an animal undergoing progressive asphyxia, or a man in a rebreathing test, actually maintains an undiminished consumption of oxygen up almost to the point of collapse and death. Those who lay stress on the increase of lactic acid under oxygen want generally fail to note that there is no accompanying decrease in the combustion going on in the body. The analogy of a smoky fire fails to explain the effects of oxygen want in the body. When an actual deficiency occurs, and the venous blood contains no oxygen whatever, death is almost immediate.

As the "hyperpneia" produced in overworked muscles, not only increases breathing, but also raises arterial pressure, it is probably related to the substances produced in the kidney when the blood supply to that organ is restricted. This substance "renin" has been shown by Goldblatt and his associates to induce hypertension.

RESPIRATION UNDER INTENSE MUSCULAR EXERTION

The distinction between the amount of stimulus to the respiratory center and the degree of excitability of the center to that stimulus is strikingly shown when we compare the breathing in a man during moderate muscular exertion with that when he makes an intense muscular exertion. In the first condition the volume of breathing is increased so nearly in proportion to the production of carbon dioxide that the percentage of carbon dioxide in the alveolar air of the lungs is nearly the same as during rest. A man walking at his normal gait scarcely realizes that he is breathing more than at rest, although actually the volume may be twice as great, or even more. But when the exertion reaches an energy expenditure and demand for oxygen of several times over the amounts involved during rest, respiration undergoes a

change. The man now over-breathes: the volume of air with which he ventilates his lungs is so large that, although the production of carbon dioxide is greatly increased, even this large amount may be diluted down to a much lower tension in his lungs than that which prevailed during rest and moderate exercise.

This relation has been particularly well demonstrated by Douglas in many experiments upon himself. He can walk at any pace up to five miles an hour with almost perfect adjustment of his breathing to the amount of carbon dioxide produced in his muscles. His alveolar carbon dioxide remains practically unchanged from the resting value. But when, during 15 minutes, he repeatedly ran up and down three flights of stairs as rapidly as his powerful legs would carry him (40 feet vertically in 45 seconds), the excitability of his respiratory center was so much increased that even 20 minutes after the exertion was ended the tension of carbon dioxide in his lungs was still considerably decreased. By that time his production of carbon dioxide had fallen again nearly to the rate previous to the muscular exertion; and he was breathing quietly. Yet the volume breathed was distinctly greater than before, for his alveolar carbon dioxide was still held below its normal resting value.

It is such experiments as this, that some investigators still interpret as indicating an "acidosis" because, during the recovery period, the blood contains an increased amount of lactic acid and the pH is lowered. But a more than normal concentration of H ions (low pH) means only that the H_2CO_3 in the blood is high in relation to the BHCO_3 . It never under any conditions means anything else. After a vigorous muscular exertion the BHCO_3 is lowered. The H_2CO_3 is also lowered, but not so much as the BHCO_3 : hence a state of so-called "uncompensated acidosis"

in which the concentration of H ions is above the normal figure. All of this is best explained by alterations in the excitability of the respiratory center: over-breathing during exertion inducing a decrease first of H_2CO_3 and then of $BHCO_3$, plus an increase of lactic acid; followed by a compensatory state in which the factors are reversed after the exertion is ended.

TESTS OF AVIATORS ON THE REBREATHER

The largest number of experiments that have ever been carried out on oxygen want and its effects on respiration were those on candidates for the air service of the United States Army during the War. For this test, I introduced apparatus that we called "rebreathers." Each contained about 100 liters of air which the candidate rebreathed through a cartridge of alkali. As the oxygen was consumed, a spirometer at the top of the apparatus gradually sank, while its up and down movements recorded the rate and volume of the man's breathing. The tests lasted only 20 to 30 minutes. The object was to determine each man's "ceiling": that is, not the altitude at which the man could stay, but that to which he could not fly for more than a few minutes without physical and mental failure and danger of crashing.

In all cases the rebreathing was continued until the man fainted or became unconscious, rigid and glassy eyed, and further continuance would have risked life. Some men failed at oxygen tension of only 12 per cent of an atmosphere corresponding to an altitude of 15,000 feet. Others lost consciousness only as the oxygen fell to 6 per cent of an atmosphere, a virtual altitude of nearly 30,000 feet. Others again failed at all gradations between these extremes.

All the men thus tested had been subjected to careful medical

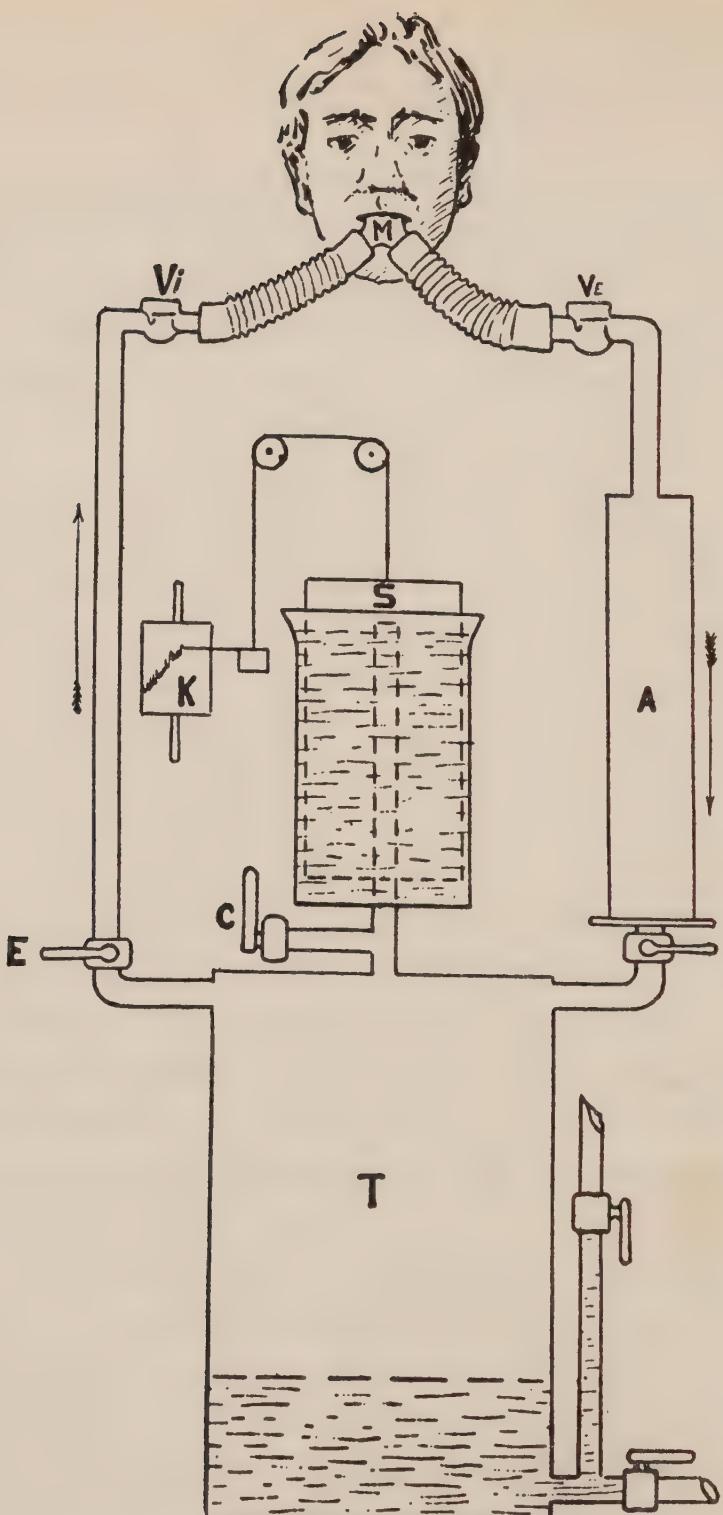


FIG. 3. The "rebreather" used for determining the ability of aviators to withstand low oxygen. The tank, T , has a capacity of 120 liters; the volume of air in it is determined by the amount of water. The man under examination has a clip on his nose (not shown), and continually rebreathes the air of the tank through a mouthpiece and the inspiratory and expiratory valves, Vi and Ve . The movements of respiration are recorded by the spirometer, S , writing on a smoked drum, K . The exhaled carbon dioxide is taken up by sodium hydroxide in the absorber, A . As the oxygen is consumed and the air volume is thus reduced, the spirometer falls and the graphic record on the smoked drum rises, indicating the "virtual altitudes" attained.

examination; all had sound hearts and lungs. The point of failure appeared to have no relation to the muscular development of the individual. The differences in their "ceilings" therefore presented a highly interesting problem; but a problem that the War would not wait for us to solve. Even so, Schneider, who was in charge of the physiological side of these tests, noted the highly significant fact that some men began to breathe a distinctly larger volume of air under even a decrease of oxygen tension as slight as only one or two per cent of an atmosphere: that is, 19 or 20 per cent instead of the initial 21 per cent. And as the oxygen tension fell further, the volume of breathing increased correspondingly. It was the men of this hyperpneic type who lasted to the lowest tensions of oxygen. They contrasted sharply with those of the non-hyperpneic type at the other end of the scale, who showed no increase of breathing, and who collapsed long before tensions of oxygen were reached that corresponded to extreme altitudes.

Recently Christensen and Krogh have carried this study a step further and have shown that the critical factor is, not the tension of oxygen in the air inhaled, but the tension maintained in the lungs. On this basis all healthy young men, as they find, fail when the tension of oxygen in their lungs falls below 35 mm. or about 5 per cent of an atmosphere. Those who, without acclimatization, can withstand the lowest oxygen in the inhaled air, and can fly safely to the greatest heights, are those who are most sensitive to even a slight decrease in the tension of oxygen. It is in these men that the hyperpneic reaction to low oxygen develops most readily.

How then shall this hyperpneic reaction be explained? It is certainly not due to any alteration in the blood in the acid direction. On the contrary, the over-ventilation renders the blood

distinctly more alkaline. This was decisively demonstrated on 9 aviators among those whom we tested on the rebreather during the War and in whom we found a marked capacity for anoxic hyperpnea. These men were tested also in a steel chamber in which the air was quickly evacuated down to half the outside barometric pressure and held at that pressure for at least an hour. The observations on one case, typical of all, are shown in table III.

The hyperpnea in this and the other cases was certainly due either to the direct influence of anoxemia upon the sinus caro-

TABLE III

Showing the influence of diminished tension of oxygen on the respiration, alveolar air and blood of an aviator

TIME minutes	BAROMETER mm.	ALVEOLAR AIR		BLOOD CO ₂ CAPACITY vols. per cent	RESPIRATION, PER CENT OF NORMAL	pH
		O ₂	CO ₂			
0	760	99	37	58	100	7.40
19	380	42	32	—	115	7.50
73	380	36	31	—	119	7.51
99	760	98	40	57	92	7.38

ticus, and so upon the respiratory center; or else to the production of hyperpnein in the tissues and its action then upon the sinus caroticus, as in vigorous muscular exertion.

Another observation of high significance made during our work with the rebreather, and mentioned above, was the extent to which the consumption of oxygen in the body is independent of the supply. It has long been known that a man breathing pure oxygen consumes no more than when breathing mere air, containing only 21 per cent of oxygen. But it was not realized that the same rate of consumption continues even into extreme

anoxia. Yet such proved to be the case. The movement of the spirometer of the rebreather was recorded on a revolving drum. As the oxygen of the air in the apparatus was consumed the spirometer sank; and the graphic record showed both the depletion of oxygen in the air that the man was breathing and the amount of oxygen that he was consuming each minute. As the slope of the record was always uniform from start to finish in every case the records demonstrated that the consumption was unchanged right down to the point at which the man collapsed in anoxia.

These were, I believe, the first determinations of oxygen consumption by means of graphic records. The rebreather was much simpler than the apparatus previously employed by Benedict for purposes of investigation. Shortly after the War he introduced the rebreather into medical use for the measurement of general metabolism.

HOW THE ALKALI OF THE BLOOD IS CONTROLLED

From the foregoing discussion and illustrations it is clear that fundamentally the tension of oxygen in the blood determines the volume of breathing, the tension of carbon dioxide in the lungs and the H_2CO_3 of the arterial blood. But how does the tension of oxygen control the blood alkali? How does a lowered tension of oxygen induce the decrease of alkali that commonly accompanies hyperpnea? How does the mountaineer become acclimatized? Why does the athlete after a contest have a lowered blood alkali and an increase of lactic acid? Why does the diabetic in coma, who exhibits Kussmaul's "fearful terminal dyspnea" as he passes into coma, develop also an extremely low alkali? How, in all these and other conditions, is the alkali of the blood decreased, if it is not neutralized by acid? And in par-

ticular, how is the alkali (BHCO_3) so adjusted to the carbon dioxide (H_2CO_3) as to maintain within narrow limits the concentration of H ions in the blood?

At least a partial answer is afforded by observations that Haggard and I published in the Journal of Biological Chemistry in 1920 under the title: "Respiratory Regulation of the CO_2 Capacity of the Blood": in other words, the control of the blood alkali by breathing. This control is the exact opposite of the control of breathing by the reaction (pH) of the blood.

We then showed that if the tension of carbon dioxide in the lungs is increased alkali is "called into the blood;" and that if the tension is decreased, alkali is "driven out of the blood." And in each direction, inward from the tissues to the blood or outward from the blood to the tissues, the shift tends to go on until the bicarbonates (BHCO_3) are so much increased or decreased that they again balance the amount of carbon dioxide (H_2CO_3) that the ventilation of the lungs maintains in the arterial blood. And when the balance is thus reestablished, the requirements of the equation

$$\frac{[\text{H}_2\text{CO}_3]}{[\text{BHCO}_3]} \times K = [\text{H}]$$

are satisfied by such values that the concentration of H ions is normal.

Regarding this shift of alkali in and out of the blood it is to be noted that the tissues of the body are many times as voluminous as the blood. McLeod showed that, if alkalis are injected into the blood, the tissues produce lactic acid to neutralize them. Sacks and Sacks have found that lactic acid diffuses so slowly that its concentrations in the blood and tissues may be widely

different. It is well known also that hemoglobin has an enormous capacity to take up and give off base under variations of pH. In fact, as Greenberg and I have recently found, the total capacity of hemoglobin for alkali is about 16 times as large as its capacity for oxygen. In blood the hemoglobin is only a little more than half saturated with alkali. And of the entire alkali of the blood, about 80 per cent is normally held by hemoglobin and only 20 per cent is in the form of bicarbonates.

The sum and substance of all this is that both disturbance of the pH of the blood by low oxygen and restoration of a normal pH are actually effected in a manner that is almost exactly the opposite of that heretofore generally believed in. It was supposed that even a slight oxygen want disturbed the oxidation in the tissues; that lactic acid diffused readily into the blood; and that respiration was stimulated in an effort to restore the normal acid-base balance. Instead, as we now see, oxygen want first alters the excitability of the respiratory center; respiration then by over-ventilation throws the relation of H_2CO_3 : $BHCO_3$ in the blood out of balance; and the tissues, through a shift of alkali, restore the balance.

When the mountaineer passes from one barometric pressure to another, either up or down, the excitability of his respiratory center is increased or decreased; and in time all the other readjustments follow. The initial cause is decrease or increase of the tension of oxygen. Yet it is not the oxygen alone, but the relation of the tension of oxygen to the amount of alkali in use in the blood, that influences the excitability of the center. Both in the ascent and descent this relation is disturbed; but as acclimatization develops it again becomes normal through the decrease or increase of alkali in the blood. The excitability is

then again also normal. If $[O_2]$ expresses the oxygen tension, $BHCO_3$ the alkali and E_H the excitability of the respiratory center, the relations may be indicated by the expression,

$$\frac{[O_2]}{[BHCO_3]} \propto \frac{1}{E_H}$$

Oxygen want is by no means the only condition that increases the excitability of the respiratory center. Fatigue, lack of sleep, and anxiety also lower the alveolar carbon dioxide and, more slowly, the blood alkali. More strongly acting are acute pain, fever, alcoholic intoxication, and the excitement stage of ether anesthesia. Following these conditions, or any other that has lowered the blood alkali, the return of respiration toward normal involves for a time a state in which the relation of H_2CO_3 : $BHCO_3$ is high, and the pH therefore low, not because the H_2CO_3 is high, but because the $BHCO_3$ is low. And it is this state that is mistakenly called "acidosis" by those who fail to realize how completely respiration dominates the acid-base balance of the blood.

On the other hand, high oxygen, sleep, and especially morphine, are among the conditions that lessen the excitability of the respiratory center and tend to raise the alveolar carbon dioxide and, more slowly, the blood alkali also.

CONFIRMATION FROM COPENHAGEN

What is set down in this chapter is in certain features antithetic to the conceptions that have long prevailed in biochemistry, particularly as those conceptions are applied to clinical conditions. It was therefore with feelings like those of Robinson Crusoe, when a sail appeared on the horizon, that, just as I was writing this chapter, there came to my desk some recent

numbers of the Skandinavisches Archiv für Physiologie. There in a group of papers dealing with severe muscular work and related topics by several investigators of the great school of physiology at Copenhagen I found observations and ideas akin to my own. Particularly in a paper on the regulation of breathing in man, based both on a critical review of the literature and on extensive experimental investigations on men and animals, Nielsen finds as follows:

- (1) That there is no evidence of any acidotic process in the respiratory center.
- (2) That oxygen want acts, not through a production of acids, but by altering the excitability of the respiratory center.
- (3) That, in agreement with the earlier observations of Ege and Henriques, oxygen want tends to induce over-breathing and consequently a variation in the reaction of the blood, not toward acidity, but toward greater alkalinity.
- (4) That, also in agreement with Ege and Henriques, inhalation of carbon dioxide is more effective in increasing breathing than is ingestion or injection of acid.

From the last of these findings Nielsen infers that the stimulation of respiration by carbon dioxide need no longer be considered as exerted through the H ions of the blood, as Winterstein and others have held; but that its influence is specific. Only on this interpretation I cannot quite agree; for the theory of control through the H ions does not require that a certain pH shall induce a certain volume of breathing.

DOES CARBON DIOXIDE ACT DIRECTLY OR THROUGH pH?

Some physiologists have answered this question in one way; some in the other way. Others again have held it to be unanswerable, since any alteration of the carbon dioxide in the blood

flowing to the respiratory center alters the pH also. But to me the outstanding fact seems to be that in acclimatization to all altitudes, from sea level up to those of the Andes and the Himalaya, the relation $H_2CO_3:BHCO_3$ and the pH in the blood are regulated much more nearly to constancy than is the H_2CO_3 alone. What we have to explain is why there are, nevertheless, considerable deviations from constancy of pH.

In a normal man or animal the relation $H_2CO_3:BHCO_3$ is approximately 3:60, and gives the blood a pH of 7.35. If by injection or ingestion of acid (HCl) we decrease the $BHCO_3$ to 40, respiration would have to increase enough (150 per cent of normal) to keep the H_2CO_3 down to 2 in order to afford again a pH of 7.35. Actually, as Haggard and I found, respiration does not increase so much, and the pH is lowered.

If, instead of decreasing the $BHCO_3$ with acid, we increase the H_2CO_3 by adding carbon dioxide to the inhaled air, the pH is again lowered. But now a decrease of pH no greater than that induced by acid is accompanied by a far greater increase in the volume of breathing. It is such facts as these that, taken apart from other considerations, seem to justify the conclusions of Nielsen and the Copenhagen school that carbon dioxide acts directly upon respiration instead of indirectly through pH.

There is, however, a factor that acts in the first of these two experiments, and not in the second. That factor is the relation of the tension of oxygen to the amount of alkali in the blood. Remembering that

$$\frac{[O_2]}{[BHCO_3]} \propto \frac{1}{E_H}$$

we see that in the first experiment the decrease of $BHCO_3$ causes an increase of the ratio of oxygen to alkali. Therefore we

should expect the decrease of excitability in the respiratory center, which in fact we find. And this decrease of excitability explains the difference in the two experiments quite as well as would the idea that carbon dioxide acts as a direct stimulant to respiration, instead of through pH.

On this question the decisive facts, to my mind, are those regarding acclimatization to altitude. They show that as acclimatization develops the excitability of the respiratory center and the pH of the blood again become nearly the same as at sea level. Yet, as the BHCO_3 is then considerably decreased, the man continually breathes considerably more air than at sea level and thereby keeps the H_2CO_3 in his blood down to the relation of carbonic acid and bicarbonates that produces the normal concentration of H ions.

Some of these relations and their variations are expressed graphically in the "CO₂ diagram" which Haggard and I first devised on the basis of the experiments reported in Table III in the previous chapter. The manner in which, in an acclimatized man, the *tension of oxygen* influences the *volume of breathing* may be represented as follows:

$$[\text{H}] \cdot E_{\text{H}} \cdot \frac{[\text{O}_2]_{760}}{[\text{O}_2]_{\text{Bar}}} \propto \text{Volume of breathing}$$

or more fully

$$\frac{[\text{H}_2\text{CO}_3]}{[\text{BHCO}_3]} \cdot \frac{[\text{BHCO}_3]}{[\text{O}_2]} \cdot \frac{[\text{BHCO}_3]_{760}}{[\text{BHCO}_3]_{\text{Bar}}} \propto \text{Volume of breathing}$$

This indicates that, if the tension of oxygen is increased, or the alkali decreased, the excitability of the respiratory center and the volume of breathing will be decreased, the H ions increased, and the pH decreased, below the values they would otherwise

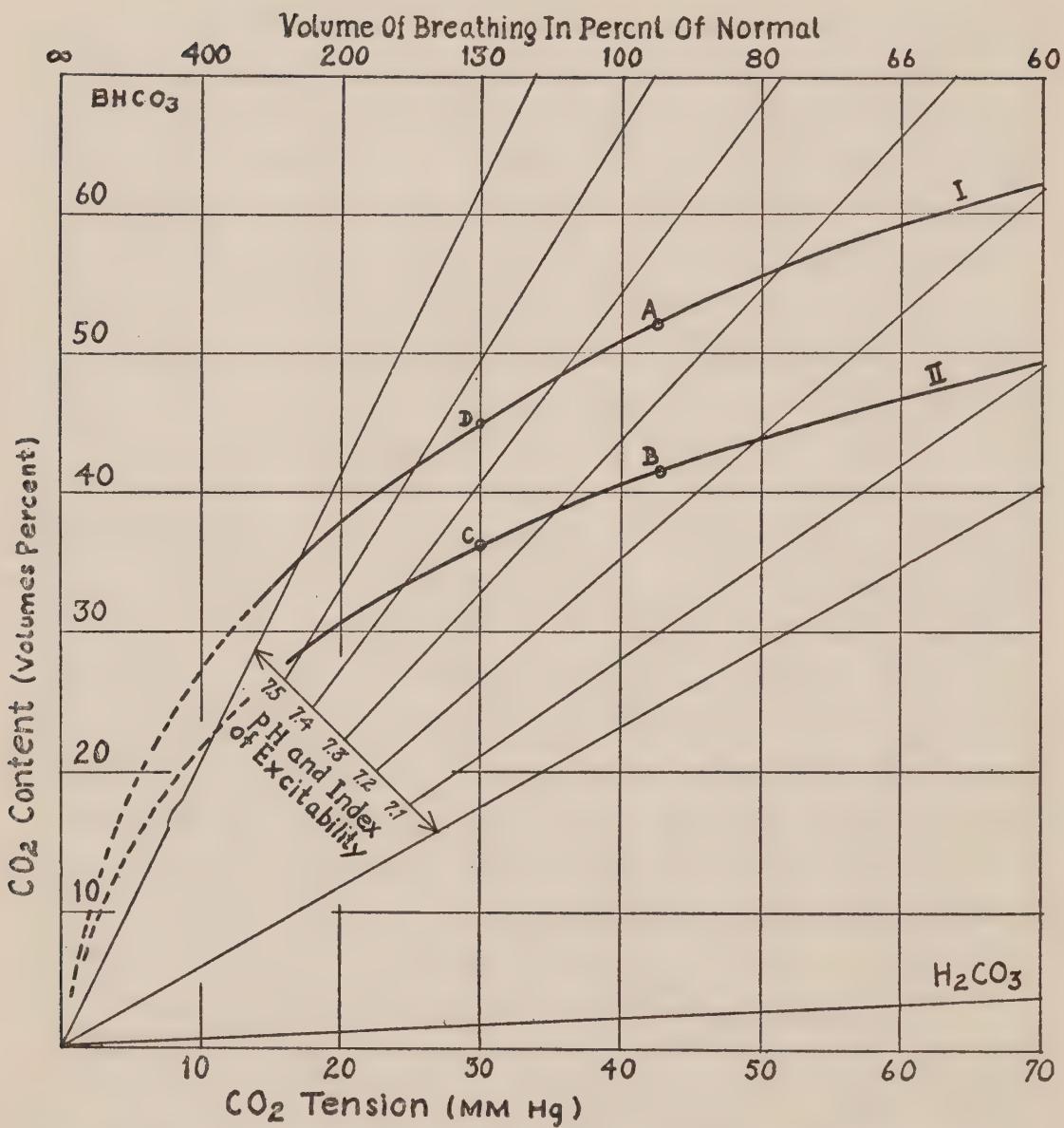


FIG. 4. The CO₂ diagram of the blood. The carbon dioxide dissociation curves, I and II, show the amounts of alkali yielded by hemoglobin to form BHCO₃ at various tensions of CO₂. At 42 mm. or 5.5 per cent of an atmosphere of carbon dioxide, curve I indicates an "alkaline reserve" of 52 volumes per cent and II indicates one of 41 volumes per cent.

The condition of the blood indicated by curve I can be changed to that of curve II in two distinct ways: either by injection or ingestion of acid, as in J. B. S. Haldane; or by overbreathing in adjustment to lowered oxygen, as in J. S. Haldane on Pike's Peak. If acid is injected, and the volume of breathing remains unchanged at 100 per cent of normal, the pH of the blood will fall from 7.35 (at A on I) to 7.25 (at B on II). If, on the contrary, the pH is held constant at 7.35 (A on I and C on II) the volume of breathing must be increased to 135. Actually under

have; and that alterations of oxygen or alkali in the opposite direction will have the opposite effects. Some day perhaps some mathematician may give us a more complete formula.

In 1915 Haldane delivered the lectures which he later embodied in his "Respiration." Among those who attended those lectures was an eminent astronomer. As he left the hall after the last lecture this astronomer remarked: "The relations of the various factors in respiration are too complicated for mere words and sentences. They should be expressed mathematically." As yet we are limited to symbolic logic.

an ample supply of oxygen the point *C* tends to move a little to the right and the resulting slight "acidosis" (low pH with low alkali) tends to "call alkali into the blood," so that the dissociation curve will gradually rise again from position II to position I. In J. B. S. Haldane the successive states of the arterial blood would be represented by the sequence *A, B, C, D, A*. In J. S. Haldane the sequence during ascent and stay on Pike's Peak and return to sea level was *A, D, C, B, A*.

If, instead of receiving acid, the man or animal is exposed to a lowered tension of oxygen, the excitability of the respiratory center is increased and with it the volume of breathing. If the volume is 135 the pH will be 7.45 (*D* on I). And alkali will be "driven out of the blood" until the dissociation curve is lowered from position I to position II. The pH will then be again 7.35 (at *C* on II) and the volume of breathing still 135. On return to a full supply of oxygen, the excitability of the respiratory center is lowered again to normal and the volume of breathing is again 100 per cent of normal. But as *C* moves toward *B* the pH of the blood is below normal and "alkali is called in" as before. All of these changes may be quite rapid except the shifts of alkali, which may require days, or even weeks, in the process of acclimatization to low oxygen at great altitudes.

This diagram shows that the deus ex machina that controls the volume of breathing and the carbon dioxide, alkali, and pH of the blood, is the excitability of the respiratory center; and that the influence that chiefly affects the excitability is oxygen. Among other influences, that may increase or decrease the excitability of the center, are lack of sleep, anxiety, pain, alcohol, ether, morphine and other anesthetics and hypnotics.

It really does not make much difference whether we consider carbon dioxide or pH as the specific stimulus to respiration, since carbon dioxide is the most active factor in the pH. But the adoption of pH in this rôle affords a more elegant conception and more rigorous definition of the hematorespiratory relations.

For a fuller discussion of this diagram and the data upon which it is based see Haggard and Henderson, *J. Biol. Chem.* 1918, 33, 333, 345, 355, 365; 1919, 39, 163; 42, 237; 43, 3; 44, 131; 45, 189, 199, 209, 215, 219; and 47, 421, and Henderson, *Physiol. Reviews*, 1925, 5, 131.

Chapter V

MOUNTAIN SICKNESS AND ACCLIMATIZATION

TO CLIMB Mount Everest and stand on the highest point on the surface of the earth has been the ambition of some of the ablest mountaineers. Yet, in spite of repeated attempts, it is an ambition that is still unattained; and that may perhaps remain forever unattainable. As a problem in climbing, the ascent offers no difficulties greater than have been overcome on scores of other peaks. But in addition there are involved difficulties and a problem due to the relation of the living body to the atmosphere, and particularly to the interaction between oxygen and carbon dioxide in breathing. Deficiency of oxygen defends the Peak against the assault of mountaineers. But that is not its sole defense. Oxygen could be supplied, were it not that the influence of carbon dioxide upon respiration at great altitudes prevents the effective use of oxygen.

Mountaineering—particularly the expeditions to Everest and other peaks in the Himalaya—affords the best of all illustrations of the fundamentals of respiration and asphyxia. Mountain sickness is a form of asphyxia. Acclimatization is a functional adjustment to counteract the lowered tension of oxygen. It is in the gradations between these two states that the physiology of altitude is especially instructive. The baby that is stillborn, the man who bleeds to death, the miner who collapses in “black damp,” the victim of carbon monoxide, even the aviator who loses consciousness as he rises toward the stratosphere, show no gradations suitable for analysis. All these forms of asphyxia contrast sharply with the state of the normal healthy individual.

It is only when we follow the members of an expedition that

starts from sea level and climbs, week after week, up into Tibet, and then day after day higher and higher on the slopes of Everest, that we see the gradations of asphyxia and the adjustments that the living body makes to protect itself against anoxia. In the slow ascent to the camp at the base of Everest, 16,500 feet, which is itself at a greater altitude than any of the summits of the Rockies or the Alps, the members of the expeditions generally experience little discomfort. Day by day the decreasing tension of oxygen increases the excitability of the respiratory center, and the volume of breathing. The tension of carbon dioxide in the lungs is correspondingly decreased; and the decrease of oxygen is thereby in part counteracted. There is also an increase in the red corpuscles and oxygen capacity of the blood. Aside from some breathlessness, particularly on exertion, the men feel as well, and to all intents they are as healthy, as at sea level.

Yet their states at each of the various altitudes, to which they become acclimatized during their slow march upward to the plateau of Tibet, are all different from that at sea level; and different also from each other. At each particular altitude respiration is adjusted to maintain a particular tension of carbon dioxide in the lungs by a corresponding volume of breathing. And it is this adjustment of sensitivity to carbon dioxide that provides for a higher tension of oxygen in the lungs than would otherwise exist. If men are healthy, and virtually normal in all these states, what then is normality? Certainly it cannot properly be defined merely as that volume of breathing, those tensions of oxygen and carbon dioxide in the lungs, and that amount of alkali in the blood that a healthy man has at sea level. It must consist rather in nearly uniform relations between the breathing and the blood that hold true at sea level, and almost true also at progressively increasing altitudes, subject only to

increasing strain with each decrease in the barometric and oxygen pressure. These relations are 100 mm. of oxygen in the lungs with 40 mm. of carbon dioxide, and 50 volumes per cent of bicarbonate in the blood; and as the oxygen falls with increasing altitude the carbon dioxide and alkali are lowered proportionally.

There is no such thing as a general acclimatization. There are as many acclimatizations as there are altitudes at which a man can live. Each is an adjustment of the carbon dioxide and alkali to correspond with a certain tension of oxygen, and each state requires time to develop. Acclimatization fails to develop only when the altitude is so great, and the tension of oxygen so low, that adjustment becomes physically impossible.

MOUNTAIN SICKNESS AT MANY ALTITUDES

Very different is the picture of the mountain sick man who has passed quickly from a lower to a much higher level. His condition presents the most interesting of all forms of asphyxia. I have seen men, and particularly women of poor physique, who were distinctly mountain sick on coming, in a day, from sea level to Colorado Springs, an altitude of only 6,000 feet. I have seen many who were perfectly acclimatized to 6,000 feet, but who became sick when transferred by the cog railroad to the summit of Pike's Peak, 14,000 feet; and many more who collapsed and fainted after making the ascent on foot. Men acclimatized to 14,000 feet, if they climb in a day to 21,000 feet, are almost certain to be mountain sick. The advance parties that become fairly well adjusted to the altitude of 21,000 feet on the North Col of Everest are liable to be again affected at first when they climb to 25,000 or 26,000 feet. And Mallory and Irvine, who had developed at least partial adjustment to the altitude of the upper slopes of Everest, probably died of asphyxia not far below the 29,000 foot summit of Everest.

All the ill effects of decreased barometric pressure depend fundamentally on the decrease in the tension (partial pressure) of oxygen. This fact was first demonstrated by Paul Bert sixty years ago and has been confirmed by all that has been learned since. The most striking exemplification occurred a couple of years ago, when aviators flew over the summit of Everest and experienced none of the ill effects, physical and mental, that mountaineers may suffer thousands of feet below the summit. The aviators were inhaling oxygen; without it they would have died. If they could have landed on the North Col, and had then removed their oxygen inhalators, they would soon have become unconscious in the tents of the mountaineers who had already spent several days at that altitude and were fairly fit. The altitude record of Lieutenant M. J. Adams of the Royal Air Force on May 30, 1937, was 53,937 feet. He wore a helmet and inflated rubber suit like that of a diver.

In acclimatization the functional readjustments, which to a considerable extent counteract the decreased tension of oxygen in the air inhaled, consist chiefly in an increased sensitivity of respiration to carbon dioxide. The increased volume of breathing thus induced lowers the tension of carbon dioxide in the lungs and raises the tension of oxygen correspondingly. This adjustment is more rapid than the increase of red corpuscles in the blood. The mountaineers on the North Col had in their lungs 19 mm. of carbon dioxide and 38 mm. of oxygen, which, in an acclimatized man, is adequate even for a considerable degree of physical exertion. The aviators, fresh from sea level, would have had in their lungs at first nearly 40 mm. of carbon dioxide and little more than 17 mm. of oxygen; and the tests reported in the previous chapter showed that 35 mm. of oxygen is the minimum on which an unacclimatized man can retain consciousness and the control of his limbs. The reason for the

difference in the tension of oxygen in the lungs of the aviators and the mountaineers respectively, lies therefore in the different adjustments of their respiration to its control by carbon dioxide. And in order to decrease the carbon dioxide in the lungs from 40 mm. to 19 mm., a man must breathe a little more than twice as large a volume of air.

THE WATER VAPOR IN THE BREATH

If a man's breath were not saturated with water vapor, the ascent of Everest would be much easier. At the temperature of the human body, water vaporizes to a tension of 47 mm.; and this is therefore the tension of the vapor in the lungs. Alike at sea level and at all altitudes, so long as the temperature of the body is unchanged, the tension is 47 mm. At sea level, where the barometer is 760 mm., the subtraction of 47 mm. leaves 713 mm. for air in the lungs. But at 21,000 feet, where the barometer is only 335 mm., the subtraction of 47 leaves only 288 for air. At an altitude so great that the barometer would be only 47 mm.—if life were there possible—the lungs would contain no air: only water vapor: that is, steam boiled off from the blood.

At all altitudes the gases in the lungs, apart from water vapor, are 80 per cent nitrogen, and only about 20 per cent of a mixture of carbon dioxide and oxygen. Now 20 per cent of 713 mm., as at sea level, affords plenty of room, so to speak, for both oxygen, 100 mm., and carbon dioxide, 40 mm. But 20 per cent of 288 mm. as on the North Col of Everest, is only 57 mm., so that if the carbon dioxide were 40 mm., as at sea level, there could be only 17 mm. of oxygen in the lungs. And a few thousand feet higher there would be no oxygen at all. Evidently then, if a man is to live at such altitudes, he must breathe a much greater volume of air than at sea level; and by means of this greater

volume of ventilation he must decrease the tension of carbon dioxide sufficiently to leave room for oxygen. Even if he breathes more than twice the sea level volume, and thereby decreases the tension of carbon dioxide in his lungs well below 20 mm., there can be room only for about 37 mm. of oxygen. And 37 mm. of oxygen in the lungs will barely maintain consciousness in an unacclimatized man.

These relations—altitudes in feet, pressures in millimeters of mercury, and volumes of breathing in per cent of sea level values for the same mass of carbon dioxide exhaled—are approximately as follows:

PLACE	ALTITUDE	BAROME-TER	LUNG ATMOSPHERE				Volume of breathing	Rest	Exercise			
			Water vapor	Car-bon diox-ide	Oxygen							
Sea level.....	0	760	47	42	100		100	600-800				
Colorado Springs.....	6,000	620	47	36	79		116	696-928				
Pike's Peak.....	14,000	460	47	28	53		150	900-1,200				
North Col of Everest....	21,000	335	47	19	39		221	1,326-1,768				
Summit of Everest.....	29,000	240	47	15	24(?)		280	1,680-2,040				

In these figures the relations are essentially: (Bar.—47) \times 0.2 = $\text{CO}_2 + \text{O}_2$. The relations of the pulmonary carbon dioxide to oxygen, which at sea level are 4:10 or 1:2.5, under the increasing strain of altitude become 6:10 or 1:1.66. The volume of breathing required to eliminate any given amount of carbon dioxide is always inversely proportional to the tension of carbon dioxide thereby maintained in the lungs. When the production of carbon dioxide is increased by exercise, the volume of breathing is increased proportionally: or more than proportionally, if the influence of a deficiency of oxygen is added.

WHY OXYGEN HELPS SO LITTLE

If one of the aviators, whom we have imagined as landing on the North Col at 21,000 feet and collapsing from lack of oxygen, were instead to continue to breathe from his inhalator—provided it was of the closed circuit type, not too heavy, and contained sufficient oxygen to last the trip—he could easily climb the remaining 8,000 feet to the summit of Everest. To do so would be no more arduous than for him to climb from sea level to the summit of a mountain similar in configuration to the peak of Everest and rising only 8,000 feet from the sea. If his supply of oxygen failed, he would probably die. But, barring that risk, he could have the credit of the “first ascent.”

Why then cannot the acclimatized mountaineer also put on an inhalator and climb straight away to the summit? The reason is that under any exertion he is more easily, and far more intensely, “out of breath” than if unacclimatized. Because of his increased sensitivity to carbon dioxide he would breathe a much larger volume of air even while wearing an inhalator.

In climbing, a man—whether acclimatized or not—produces six to eight times as much carbon dioxide as he does at rest; and to maintain the carbon dioxide in the lungs at the same tension as during rest, the volume of his breathing must be proportionally increased. The aviator on Everest wearing an inhalator would maintain a tension of 40 mm. of carbon dioxide in his lungs—the same as at sea level; and in doing so he would breathe 6 or 8 liters of air per minute during rest, and six or eight times as much—that is, 36 to 64 liters per minute—when climbing. As a vigorous man easily breathes so much, his respiration would not be extremely oppressed even if he ascended at a good pace.

On the other hand, the mountaineer with his respiration adjusted to the altitude of the North Col of Everest maintains the

tension of carbon dioxide in his lungs at about 20 mm. He produces the same amount (mass) of carbon dioxide as at sea level; but in order to dilute this carbon dioxide from 40 mm. down to 20 mm. he has to breathe twice as large a volume of air—that is, 12 to 16 liters per minute—in which to dilute and exhale it. He does this quite easily during rest. But when he climbs and increases his production of carbon dioxide six or eight times, he must breathe six to eight times as much air as during rest: that is, 72 to 126 liters per minute. Otherwise the carbon dioxide in his lungs will rise above 20 mm. and cause a fearful dyspnea. This is what acclimatization costs him, even though he wears an inhalator and has plenty of oxygen. Any deficiency of oxygen increases his breathing far beyond even these figures, and thus adds acapnia to anoxia. No man can maintain such respiration for long without collapsing. The twin defenders of Mount Everest are oxygen and carbon dioxide.

TYPES OF INHALATOR

Two types of inhalator are available. In one type the oxygen from a steel cylinder is supplied to a mask or bag into which air also is admitted and from which the expirations escape. Such an "open circuit" inhalator gives some benefit during rest and relatively quiet breathing; but it is of little or no assistance in climbing. The few liters of oxygen a minute that it supplies are merely blown away in the hurricane of breathing; and the increase of oxygen, over that in the air, that reaches the lungs is negligible.

The other type of inhalator is similar to those used by rescue crews in poisonous atmospheres in mines. In such a "closed circuit" inhalator all the oxygen consumed by the wearer is supplied by the apparatus; none from the outside air. The car-

bon dioxide is absorbed with soda lime. The apparatus is heavy; and the volume of oxygen in steel cylinders and amount of soda lime in tin canisters that a man can carry are sufficient for only two or three, or at most, four or five hours. If such an inhalator were used from 21,000 feet or 23,000, or even from 25,000 feet, to the summit of Everest and return—that is, for a period of seven or eight hours or longer—it would require several renewals of the cylinders of oxygen and the canisters of soda lime. The ascent of Everest would then become a problem of supply: a problem of extreme practical difficulty. Yet, if attacked by any other means, Everest will probably exact a toll of many more lives before it is conquered: if ever.

Other means offer no aid. Acclimatization to a great altitude involves a functional adjustment that is gradually acquired and as gradually lost. It is not to be gained by swallowing some ammonium chloride. Nor can it be reversed by a dose of sodium bicarbonate. Whymper on Chimborazo (20,500) swallowed some potassium chlorate for an extra supply of oxygen. But it probably merely converted some of his hemoglobin into methemoglobin, and decreased the oxygen-carrying power of his blood. Childs and Hamlin tried the inhalation of a little carbon dioxide on Pike's Peak, and obtained results suggesting that it might be of some use for aviators between 10,000 and 15,000 feet. But mere increase of breathing will not save either aviators or mountaineers at such altitudes as those of Mount Everest. Nature is not easily circumvented.

ALTITUDE AND THE RESPIRATORY CENTER

It is one of the most surprising facts in altitude physiology, as in other forms of asphyxia also, that a decreased pressure of oxygen does not appreciably decrease the amount of oxygen con-

sumed in the body or the amount (mass) of carbon dioxide produced. After an acute asphyxia and sometimes even during mountain sickness, the combustion is increased and fever develops. Under less severe conditions the amounts of oxygen consumed and carbon dioxide produced remain essentially the same as under normal conditions at sea level. A lower tension of oxygen in the lungs is due only to a lower tension in the air inhaled. A lower tension of carbon dioxide, on the contrary, is due to an increase in the volume of breathing. If the volume of breathing is increased, we must look to the respiratory center for the underlying reason; and we find that, at least while acclimatization is developing, there is an increased excitability.

Two facts support this explanation. One is, that the greater the altitude to which a man is acclimatized, the shorter is the time that he can hold his breath: 40 to 60 seconds at sea level; 10 or 15 seconds on Pike's Peak, and probably only 4 or 5, if so long, on the shoulder of Everest. This shortening of the apnea is, however, in part due to the fact that the lower the tension of carbon dioxide required to stimulate breathing the shorter the time required to accumulate that tension in the lungs.

The other fact, indicating increased excitability, is that during the days or weeks in which acclimatization is developing, there is continual overbreathing so that the pH of the blood is continually on the alkaline side of neutrality. This lowering of the concentration of H ions is indeed the means by which a part of the alkali of the bicarbonates is at first transferred to hemoglobin, while more is driven out of the blood into the tissues. The observations of Barcroft, and of Hasselbalch and Lindhard, indicate that after acclimatization to any altitude is fully developed, the pH of the blood tends to become again nearly the same as at sea level. In other words, the BHCO_3 of the blood is de-

creased—by passage into the tissues or urine—nearly as much as the H_2CO_3 is decreased by respiration.

ALKALOSIS ON ASCENT: ACIDOSIS ON DESCENT

It is during the time that the relation of $\text{H}_2\text{CO}_3:\text{BHCO}_3$ is low and the pH of the blood abnormally high—a temporary relative alkalosis—that acclimatization develops. If this adjustment during the ascent is much delayed, the man is mountain sick.

Contrariwise, it is during the time that the relation of $\text{H}_2\text{CO}_3:\text{BHCO}_3$ is high after descent to a lower altitude, where the pressure of oxygen is higher, that the adjustment of the respiratory center is reversed. Its excitability is lowered; the volume of breathing is correspondingly decreased; the H_2CO_3 in the blood is thereby again increased; the pH is moved to the acid side of the normal; and alkali is gradually recalled to the blood.

If there were ever in any condition such a state as “asphyxial acidosis,” we should expect to find it in men during ascent to great altitudes. Instead, we find “alkalosis” during ascent and “acidosis” during descent: and it is exactly during this state of “acidosis” that a man returning from a vacation spent in mountaineering feels particularly well and vigorous.

We may turn now to a consideration of less extreme conditions.

PRELIMINARY TO PIKE'S PEAK

In August 1910 the International Congress of Physiologists met in Vienna. Krogh came, fresh from two major achievements: proof that no appreciable amount of combustion occurs in the lungs, and that atmospheric nitrogen makes no reactions in the animal body. Winterstein demonstrated that injection of acid into the umbilical veins of apneic rabbit fetuses induces active

respiratory efforts: the experiment that led him to the theory that the pH of the blood is the specific stimulus for the respiratory center. L. J. Henderson presented some of his early work on ionic equilibrium, and Asher and Abderhalden debated it. And after reading my own paper on the stroke volume of the heart I was engaged with Zuntz in one of those polyglot discussions characteristic of international congresses: he in German, I in English, and neither fully understanding the other. But I know now that he was right.

Haldane and Douglas demonstrated that alveolar air from the lungs can be obtained for analysis by making a sudden deep expiration, through a wide rubber tube, and drawing off a sample of air from the end of the tube close to the lips. They showed also that apnea vera follows forced breathing, and that Cheyne-Stokes breathing may be induced in normal men by intermittent anoxia. Among those who watched these demonstrations with intense interest was Leon Fredericq. As Haldane then said to him, they confirmed the conclusion that Fredericq himself had drawn (1901) from his "crossed circulation" experiment on animals: the conclusion that it is the gases in the blood flowing from the lungs to the base of the brain that mainly control respiration.

For me the greatest event was to meet Haldane and Douglas, whom previously I had known only by their papers. All one afternoon and evening we discussed respiration; and it was during that talk that Haldane told me of his wish to spend a sufficient time on some high mountain to study the development of acclimatization. For a long stay any summit of the Alps, even in the hut on Monte Rosa, would be too harsh and arctic; the Andes and Himalaya were too far, and unprovided with civilized amenities. It was not that he objected to physical hardship, but that cold, exertion and bad food would vitiate the evidence

regarding acclimatization to low oxygen. "I want a nice comfortable, easily accessible, very high mountain with a fairly good hotel on the top," said Haldane. And I replied: "Come to America next summer and we will spend a month or two on the top of Pike's Peak."

THE PIKE'S PEAK EXPEDITION

Eleven months later we met, as agreed, in Colorado Springs. There E. C. Schneider joined us; and on July 12, 1911, we four boarded one of the obliquely built passenger cars, in front of an oblique little steam engine on the cog-railway; and in an hour and a half we were pushed up to the summit of Pike's Peak. At 11 o'clock we were unloading our cases of apparatus on the terrace in front of the Summit House, prepared for a five weeks' stay. We were the first well-equipped group of scientists who were prepared to observe the effects of low barometric pressure—that is low oxygen—uncomplicated by the effects of the physical exertion involved in gaining the altitude on our own legs. Our altitude was 14,100 feet, a little more than that of the Jungfrau, a few feet less than that of the Matterhorn, and only 1,000 feet less than Mont Blanc. The barometer was 460 mm.: 300 mm. less than at sea level.

For the first hour or so after our arrival, we were all very cheerful, unpacking apparatus and fitting up the room that was to be our laboratory. Then one after another, my three comrades began to exhibit in their mental attitude the blueness which was already a striking feature of their lips and faces. Dinner did not interest them; society was unwished for. The question which seemed principally to concern them was whether they should betake themselves to bed, or, in the language of the ocean-liner, should "go to the rail." Owing to a quite unusually sensitive

respiratory center, I got off much easier, and suffered with nothing more than a slight feeling of tightness across the forehead. Haldane, who was next best, was quite uncomfortable for a day or two. Douglas was speechlessly miserable until the third day. And Schneider for the better part of a week suffered from intense frontal headache, nausea and sleeplessness.

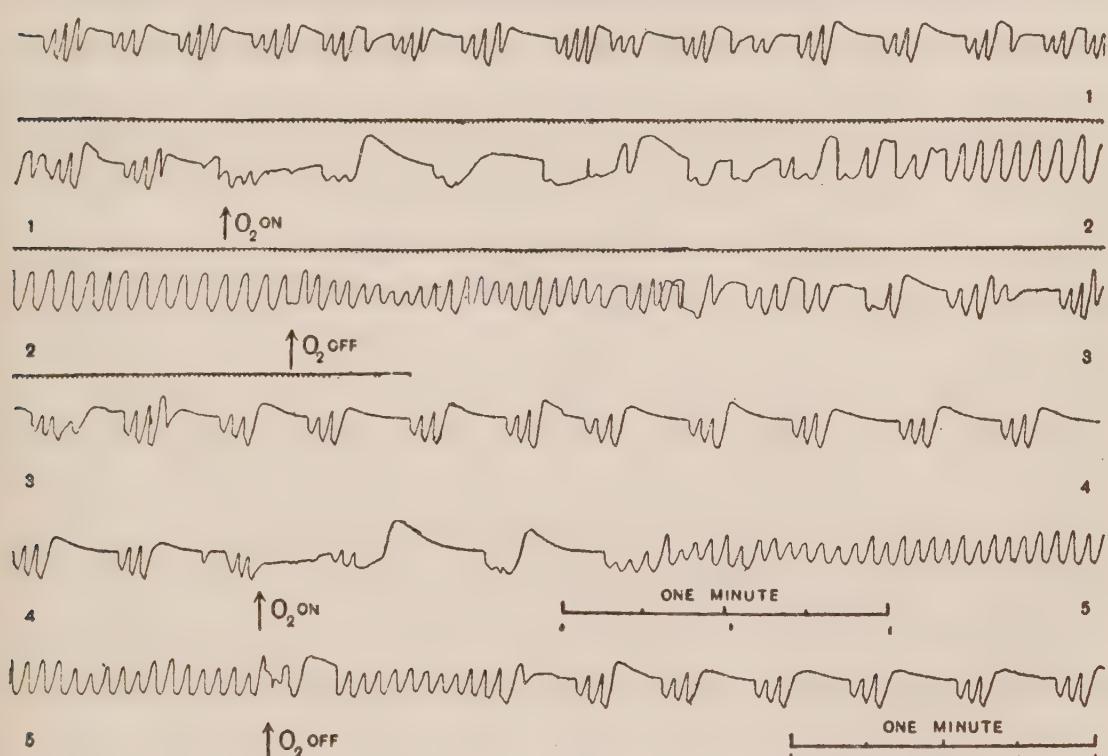


FIG. 5. Graphic record of periodic, or Cheyne-Stokes, breathing in Henderson on July 27, 1911, after climbing a height of 1200 feet in 25 minutes near the top of Pike's Peak, altitude, 14,100 feet. Note effect of inhalation of oxygen. Time tracing in seconds. Inspiration downward.

Although Schneider had lived for several years at Colorado Springs and made frequent tours in the mountains, he suffered more than any of the rest of us. Night after night he lay awake with a throbbing headache and listened to me,—we shared the same room—snoring in “Cheyne-Stokes” breathing. At sea level this peculiar form of respiration is characteristic of severe

heart disease; at altitudes it is common in normal men. It consists of periods of vigorous panting, alternating with intervals of complete cessation of respiration. In my case, three or four times a minute there was an apnea for several seconds, ending in a shallow breath, followed by a deeper breath, and then a tremendous gasp. After this came another period of no breathing. Nevertheless after the first week, we all slept well.

It was not only in sleep that we were subject to Cheyne-Stokes breathing. Every test of breath-holding to find the degree of acclimatization was followed by such breathing for ten or fifteen minutes. In shaving, one involuntarily holds his breath for a few seconds at a time; and it often happened that before one cheek was finished the breaking point would be reached, and the shaver would have to stop and pant awhile. Cheyne-Stokes breathing is not unpleasant; often one scarcely realizes that he is doing it. It was amusing to see a man start to light his pipe just as one of the periods of panting was coming on; for an imperious need for breathing would then compel him to take his pipe out of his mouth and let the match go out. He did not have to give up smoking, however; he needed only to wait until one of the apneic pauses came. He could then light his pipe quite easily.

ALVEOLAR AIR AND THE VOLUME OF BREATHING

The particular object of the expedition was to determine the adjustment of respiration to diminished tensions of oxygen by the new method that Haldane and Priestley had introduced six years before. This was the method of obtaining alveolar air for analysis by a sudden maximal expiration through a long tube and withdrawal of a sample of the air that—because it came out last—must have come from the depths of the lungs. For our purpose the method was ideal: far superior to any that had been

available to previous investigators. Zuntz and his companions in the Alps were handicapped and limited by the older indirect method. For them each observation, to determine the volume of breathing corresponding to a certain tension of carbon dioxide

TABLE IV

Showing the changes in the alveolar air, volume of breathing and hemoglobin of the blood during acclimatization to altitude and after return to sea level

ALTITUDE	DAYS AFTER ARRIVAL	ALVEOLAR CARBON DIOXIDE	VOLUME OF BREATHING, PER CENT SEA LEVEL VOLUME	HEMOGLOBIN, PER CENT OF NORMAL
<i>feet</i>				
Sea level	100+	40	100	100
6,000	1	37	108	100
	2	36	111	100
	3	35	115	101
14,000	1	32	125	103
	2	31	129	106
	3	30	133	108
	5	29	138	109
	10	28	143	113
	20	27	148	116
	35	26	154	120
6,000	1	29	138	112
	2	31	129	110
	3	33	121	108
Sea level	1	36	111	105
	2	39	102	104
	5	40	100	102
	30	40	100	100

in the lungs, required three determinations or estimates: the amount of carbon dioxide produced per minute, the volume of breathing per minute, and the fraction of air inhaled that takes no part in the exchange of gases because it merely fills the dead space—the mouth, nostrils, trachea and bronchi. With the new

method the alveolar air could now be obtained for analysis several times a minute, and the relation of the volume of breathing to the gaseous exchange followed as closely as desired.

One of the points of fundamental importance, which the German and Austrian investigators had already demonstrated, and which was fully confirmed by Douglas on Pike's Peak, and later by Hasselbalch and Lindhard in an evacuated steel chamber in Copenhagen, was that metabolism is independent of the tension of oxygen. The amounts of oxygen consumed and of carbon dioxide produced during rest at great altitudes are the same as during rest at sea level. With this basic fact established each determination of the carbon dioxide content of the alveolar air becomes inversely a measure of the volume of the ventilation of the lungs in comparison to the ventilation at sea level.

The figures in table IV, averaged from observations on those of us who had recently come from sea level, show the course of events in three of the main features of acclimatization to altitude and again later to sea level: the alveolar carbon dioxide, the volume of breathing in per cent of sea level values and the amount of hemoglobin in the blood.

RESPIRATION UNDER EXERCISE

So much for respiration during rest. How should we breathe during moderate exercise? And how again during intense exertion? To these questions we devoted numerous tests and obtained very definite answers that are nevertheless puzzling to interpret.

For each of us there was a pace at which he could walk at sea level—five miles an hour for Douglas, and somewhat less for the rest of us—without appreciable change in the alveolar carbon dioxide from the values when at rest. In other words, the vol-

ume of breathing increased merely in proportion to the amount of carbon dioxide produced and exhaled. To our surprise we now found that, when we tramped at such paces back and forth along a level stretch of a hundred yards on the summit of the Peak, we each still maintained the same alveolar carbon dioxide as when sitting at rest in our laboratory. We were breathing during rest about 50 per cent more than at sea level; and we now found that in moderate exercise at 14,000 feet we also breathed just 50 per cent more than during such exercise at sea level. The increased consumption of oxygen and production of carbon dioxide during the exercise had exactly the same comparative effect: the alveolar carbon dioxide was held steady at both levels.

Very different were the effects of vigorous exertion. For our experiments on this subject we generally made use of the last half mile of the cog-railway where it ascends the final peak at a grade of one in four. Up this track we did numerous hundred-yard and quarter-mile dashes, and occasionally went lower down for forty or fifty minutes of violent exertion in the return to the summit. The dyspnea (panting) induced by these exercises was of terrific violence, the subject becoming absolutely speechless, while he pumped for dear life. Two such experiments on Schneider and myself were as follows:

The alveolar air and breathing during climbing. Distance 1.77 miles. Rise 1640 feet, Schneider in 43 minutes, Henderson in 55 minutes. The figures for the alveolar carbon dioxide were as follows:

	SCHNEIDER	HENDERSON	
Before start.....	30.0	27.2	Quiet breathing
40 min. from start.....	22.1	19.1	Heavy panting
7 min. after stop.....	23.7	26.1	Cheyne-Stokes breathing
40 min. after stop.....	26.7	25.8	Quiet breathing

It is noteworthy that, although by the time the last two determinations were made on each of us the respiratory storm was over, the figures show that the alveolar carbon dioxide was still much below normal; indicating the continuance of overbreathing.

Of another experiment Haldane wrote as follows:

July 22. Schneider and Henderson walked down the cog-railway about a mile (vertical distance about 1,000 feet). Returned in 30 minutes. Up the last 200 yards of track (25 per cent grade) they walked faster. Schneider led, but Henderson, who was lagging, made an extra effort, caught up, and had a few seconds of vigorous hyperpnea. He then had a fine supply of "second wind," and went with long steps up the remainder of the slope, leaving Schneider some way behind. He was then nearly knocked out, however—great respiratory distress, nearly vomited, turned an ashy gray color, knees wobbled. He managed to reach the laboratory, however. After the violent hyperpnea, there was a period of irregular apnea (that is, of no breathing whatever), and deep gasps, then Cheyne-Stokes breathing. Oxygen caused at first apnea, then regular deep breathing, very comforting and agreeable to the subject. On stopping the oxygen, Cheyne-Stokes breathing returned.

A few days later Schneider spent a few hours at the foot of the mountain and utilized the opportunity to run up a stretch of the cog-railway similar to that near the summit. Under the higher pressure of oxygen there he found that the same exertion induced much less dyspnea than at the summit. Yet a few days after that, when we all went down to stay, we found that immediately on arrival at the lower station of the cog-railway we could hold our breath no longer than at the summit.

Evidently the increased breathing of acclimatization to altitude is a condition distinct from the hyperpnea induced at both high and low levels, but especially at great altitudes, by intense muscular exertion. An athlete in training generally acclimatizes more quickly than a man of sedentary habit: but exercise does not promote acclimatization.

This distinction is further supported by the following observa-

tion: Professor F. G. Benedict had asked me to obtain some samples of air on the Peak and to send them to him in Boston for analysis. To fill the sampling tubes I used a rubber aspirating bulb. To my surprise, squeezing that bulb vigorously for a couple of minutes, until the muscles of my right forearm were somewhat fatigued, induced quite vigorous hyperpnea, followed by apnea. The actual energy expended was small compared to that of walking at a pace of four miles an hour; and yet the overworking of the small group of muscles in the forearm induced overbreathing while the moderate exercise of the large muscles of the legs did not. Evidently some substance was produced in the overworked muscles that was carried by the blood to the respiratory center and temporarily increased its excitability. That substance was probably the same as that (hyperpnein) which induced overbreathing in the classic experiments of Geppert and Zuntz on animals quoted in a previous chapter.

OXYGEN DEFICIENCY AND UNREASONABLENESS

During our stay on the Peak, hundreds of people made the ascent—by railway, on donkey back and on foot. They exhibited all degrees of mountain sickness from headache to fainting. But of all the symptoms those involving the mind, particularly the judgment and temper, were most striking and often continued to develop for some hours even after a short stay at the summit and immediate descent. Indeed, the late Professor William Bayliss, after reading the account of the expedition in the Philosophical Transactions of the Royal Society, was fully justified in the remark that: "Perhaps all unreasonable people are suffering from lack of oxygen in their brains." The observations of McFarland and his companions in the recent expedition to the Andes tend to the same conclusion.

OXYGEN SECRETION OR HYPERPNEA?

Here I shall confine the discussion to the extraordinary recovery of reasonableness, good temper and health in men, who, after being mountain sick and unreasonable for a time, develop some reaction by which their mental balance, good temper and health, are restored. They become acclimatized. Haldane believed that this reaction, of which he was the discoverer, involved a secretion of oxygen in the lungs. By oxygen secretion he meant a capacity on the part of the lungs to transfer oxygen from the alveolar air into the blood until the pressure of oxygen in the blood is higher than in that air: in other words, to make oxygen flow uphill. The technical details on which he based this claim, and the method by which he believed that he could measure the super-pulmonary pressure of oxygen in the blood are set forth in the second edition of "Respiration" which, with Priestley as co-author, Haldane completed a year or two before his death.

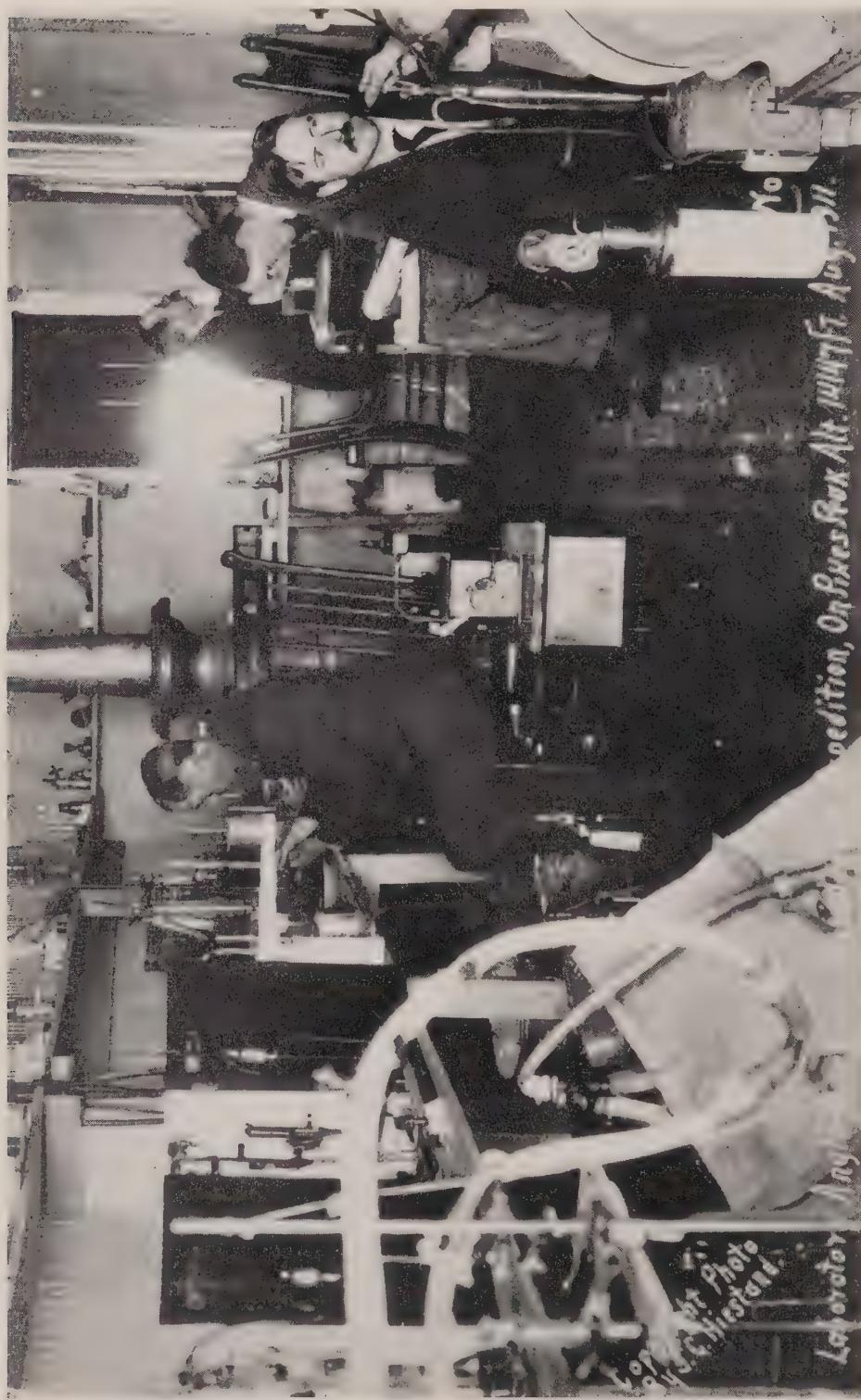
Early in his scientific career Haldane carried out extensive investigations on carbon monoxide asphyxia. In these experiments he repeatedly subjected himself and his co-worker, Lorrain Smith, to degrees of saturation with carbon monoxide such that they could only stagger home in a state which some of the neighbors interpreted as severe alcoholic intoxication. Fortunately the series of experiments was interrupted by a vacation; for, when it was resumed, a new and startling fact developed: the experimenters found that they were now far more severely affected than in the last tests before the vacation. During the earlier series, they had developed to a considerable degree the capacity to counteract the anoxemia that carbon monoxide induces. They were partially acclimatized.

The question then arose: If there is a higher pressure and a larger amount of oxygen in the blood than can be accounted for

on simple physical principles, how can that pressure be demonstrated and measured? On this point Haldane argued that, if the pressure of oxygen in the blood is raised, the amount of carbon monoxide in the blood must thereby be decreased. All that is necessary, he said, is to determine how much carbon monoxide the blood drawn from a finger contains after such an experiment, and to compare that amount with the amount in a sample of blood exposed to alveolar air in a flask. If the carbon monoxide in the one sample is less than in the other, the oxygen pressure in the pulmonary blood must be higher than that in the pulmonary air.

This was the method that he employed also on Pike's Peak to show that in men who are mountain sick there is no oxygen secretion; but that when they become acclimatized, along with other readjustments, they develop oxygen secretion. I shall always remember Haldane's figure outlined against the north window of our laboratory as he did the titration of the two samples of blood with carmine solution to measure the carbon monoxide in them. To compare the colors he would hold the test tubes up against the grey cloud that formed over the Peak each morning just before the daily snowstorm broke.

One feature of the procedure required to demonstrate oxygen secretion was, I think, particularly significant. The man under test, after his blood was about 20 per cent saturated with carbon monoxide and while breathing into an apparatus containing a small amount of carbon monoxide, was required to work a lever back and forth moving a heavy weight. The muscles of his arm were considerably fatigued, just as in my case when squeezing the rubber aspirating bulb. The work done in pulling and pushing the lever was only sufficient to double the consumption of oxygen; and walking at a pace of only two miles an hour will do



Interior of laboratory on Pike's Peak: Haldane reading barometer; Douglas calculating results; Schneider making a gas analysis; Henderson about to inhale oxygen and carbon monoxide.

as much. But, as all the work was performed by only a small group of muscles, they were sufficiently overworked to produce some substance that induced a moderate degree of overbreathing; and to induce also, if Haldane was correct, secretion of oxygen by the lungs. Certainly the color of the lips brightened; and when the samples of blood were titrated the amount of carbon monoxide in the blood that had been through the lungs was less than in the control sample equilibrated with air from the apparatus.

As all physiologists know, the theory of an active secretion of oxygen by the lungs has been vigorously combated by Barcroft. Not only the theory, but the fact of improvement in physical and mental condition, after a rather prolonged exposure to partial anoxia, is questioned. This disagreement between two master physiologists on a point of fact is, however, I think, to be explained rather on grounds of difference of respiration than of thought. Haldane was a markedly hyperpneic person. He adjusted to low oxygen quite readily. Barcroft, on the contrary, even after many days in a chamber of low oxygen, was still mountain sick. He had no considerable increase of breathing and certainly no oxygen secretion. I am confident that if the two men had been tested on the rebreather apparatus which we applied to aviators, as described in chapter IV, Haldane would have demonstrated a ceiling several thousand feet higher than Barcroft. And daily practice on the rebreather would have raised Haldane's ceiling much more readily than that of Barcroft.

The fact of such adjustment in men of highly hyperpneic type does not, however, afford proof of oxygen secretion. Improvement in physical and mental condition certainly occurs, as Haldane described it and is probably due, at least in part, to

increase of oxygen in the blood. But this increase need not involve oxygen secretion. It is always associated with an increase in the volume of breathing; and essentially the same kind and degree of improvement can be equally well induced in a non-hyperpneic man or animal by another method: a method that presumably does not involve oxygen secretion.

That method is inhalation of carbon dioxide. Haldane himself found that a mouse poisoned with carbon monoxide to the point of collapse makes an immediate partial recovery when placed in a vessel filled with human expired air. Haggard found that a dog in a small chamber with enough carbon monoxide to render the animal prostrate, again becomes conscious and gets on its feet as soon as a considerable amount of carbon dioxide has accumulated in the chamber. He also found that in an atmosphere containing a lethal amount of carbon monoxide a dog lives to a 10 or 15 per cent higher concentration of that gas in its blood when carbon dioxide is present in the atmosphere than when it is not. It is well known that in mine rescue operations and in city fires men who have been in an atmosphere of smoke, carbon monoxide and carbon dioxide, collapse when they come into fresh air, and the stimulus of carbon dioxide is withdrawn. These facts do not explain the adjustment to carbon monoxide and other forms of anoxemia that Haldane discovered. But they do indicate that the reaction may some day be explained in some manner other than by oxygen secretion.

For nearly a century the parts played by oxygen and by carbon dioxide, and their relations to each other in respiration, have been among the major problems of physiology. Haldane established the principle that the immediate control of breathing is exerted by carbon dioxide. Every text book now recognizes that. But another principle is not so generally recognized: he

proved also that the fundamental control of respiration is exerted by oxygen. The Pike's Peak Expedition afforded conclusive evidence that in adjustment alike to sea level and to a great altitude the volumes of breathing are such that the tensions of carbon dioxide and oxygen in the lungs and blood come into the relation of 40:100. FitzGerald, under Haldane's guidance, filled in the gap between sea level and the Peak by observations on the inhabitants of intermediate altitudes and showed that the same relation holds everywhere. This relation was also found by Hasselbalch and Lindhard under various pressures in a steel chamber. They even extended it to pressures higher than those of the sea level barometer. The two fundamental principles in the chemical control of respiration thus established might well be termed Haldane's laws. They are (1) that in adjustment to all altitudes and barometric pressures the tension of carbon dioxide is maintained proportional to that of oxygen; and (2) that at any one adjustment the volume of breathing is proportional to the amount of carbon dioxide produced and exhaled. Just as the control of the pH of the blood involves the maintenance of a uniform relation of $H_2CO_3:BHCO_3$, so apparently the processes of oxidation and reduction in the tissues require a uniform relation of the tensions of oxygen and carbon dioxide.

The reaction that Haldane called "oxygen secretion" is, I believe, probably dependent in some manner not yet precisely definable, upon the interaction of carbon dioxide and oxygen in the blood. In the blood, as it flows through the lungs and then through the tissues, oxygen does not merely replace carbon dioxide, and vice versa. The two gases are in fact held in quite distinct and different types of combination: oxygen combined with hemoglobin and carbon dioxide with alkali. Yet each gas

influences the amount of the other that is held at a given tension. Increase of carbon dioxide tends to decrease the amount of oxygen held by hemoglobin, and increase of oxygen tension tends to decrease the amount of carbon dioxide. These two facts of fundamental significance were demonstrated, the first by Bohr, Hasselbalch and Krogh, the second by Christiansen, Douglas and Haldane. Within the red cells there has now been found by Meldrum and Roughton a catalyst that accelerates the reaction by which carbon dioxide combines with water to form carbonic acid and by which carbonic acid is again dissociated into carbon dioxide and water. From these and perhaps other factors and reactions yet to be discovered, we may hope some day to understand how the absorption and utilization of oxygen in the blood of acclimatized men may be promoted. We may then attain a physicochemical conception of so-called "oxygen secretion."

MEMORIES OF PIKE'S PEAK

To those who were privileged to participate in the Pike's Peak Expedition the memory of that time has remained a life-long inspiration. All the surroundings were such as to deepen the impression. There was an electric storm nearly every morning during July. We could hear it coming over the mountains. If one were out of doors his hair might stand on end with static electricity, and a brush discharge crackled from his extended fingers. As the storm came nearer the lightning and thunder became simultaneous, like a big firecracker, striking all about and sometimes on the hotel; and fire balls rolled in the snow. Meanwhile we sat in the comfortable laboratory we had rigged up in our largest room and analyzed our alveolar air.

At night we watched from the terrace in front of the hotel:

the air was cool and calm, the stars brilliant overhead, and a mile or two below us, far out over the plains, electric storms flashed as they wandered. More often we sat around the big stove in the laboratory and talked of respiration. It was then that the ideas that are set forth in this book began to take shape in my mind. It was a golden time. Men who are friends under 460 mm. of barometric pressure, are friends to the end of life.

Chapter VI

CARBON MONOXIDE ASPHYXIA

CARBON monoxide is the cause of more deaths than those due to all other gases. As an industrial poison it is second only to lead. Its hazard to life can never be entirely eliminated. So long as fire is used for heat and power, and so long as combustible materials are contained in our homes, deaths by asphyxia will occur. At some far distant time all bacterial and viral infections may perhaps be eliminated, and cancer and the organic diseases controlled. But even then, it is safe to predict, men will die of carbon monoxide asphyxia.

Oxidation is one of the main processes of chemistry. The oxidation of carbon, which we call combustion, may take place in two stages: incomplete combustion, when the supply of oxygen is deficient; and complete combustion, when oxygen is supplied in excess. The incomplete reaction produces carbon monoxide; the complete reaction yields carbon dioxide.

Iron is a metal that is readily oxidized and again deoxidized. It is the constituent of the hemoglobin of the blood that endows that substance with its capacity to combine with oxygen in the lungs and to give off oxygen to the tissues. This reaction between oxygen and hemoglobin is actuated by minute differences of oxygen tension: a few millimeters more in the lungs causes oxygen to be taken up; a few millimeters less in the tissues causes oxygen to be given off. For these reactions to operate effectively the affinity between the two substances must be weak.

The same molecular constitution that endows hemoglobin with the capacity to react with oxygen enables it to react also with carbon monoxide. Unfortunately the affinity of hemoglobin

for carbon monoxide is not weak. Instead, as Claude Bernard first showed, it is many times stronger than the affinity for oxygen.

Theology once claimed that nature was designed as a setting for man. Science reversed this view, and saw man and other living beings as adapted to nature. Philosophy then suggested that the fitness of nature to produce and support life lies in the reactions of the atoms, perhaps even in the electrons. To all of these views carbon monoxide affords an outstanding objection. Apart from its reaction with hemoglobin, carbon monoxide is a harmless gas—as neutral as nitrogen. It is only by this one reaction that it becomes a prime enemy of all red blooded creatures. The use of fire was man's first successful step in controlling the forces of nature to his needs; yet it brought with it the hazard of asphyxia. As an example of lack of design, lack of adaptation and lack of fitness between man and nature, carbon monoxide is one of Nature's major mistakes.

THE ABSORPTION OF CARBON MONOXIDE

The body of an adult man of average weight contains enough hemoglobin to hold about 600 cc. of oxygen: approximately two minutes' supply. If completely saturated, the hemoglobin would hold the same amount of carbon monoxide: one molecule of carbon monoxide replacing one molecule of oxygen in the blood. The absorption of 6 cc. of carbon monoxide from the lungs produces, then, one per cent of saturation, and abolishes one per cent of the oxygen capacity.

During bodily rest the tissues extract only about 30 per cent of the oxygen in the arterial blood, or 6 cc. of oxygen per 100 cc. of blood, before it passes on into the veins, and so back to the heart with 70 per cent of its load unused: a large factor of safety.

During muscular exertion this factor of safety is drawn upon to such an extent that 70 or 80 per cent of the arterial oxygen is consumed in the tissues, and correspondingly less is carried on into the veins. For these reasons a man at rest can tolerate the abolition of 25 per cent of the oxygen capacity of his blood by carbon monoxide, and experience nothing more than a headache. If, however, he makes any considerable exertion, the supply of oxygen to his tissues is inadequate, and he faints.

The unit in which various concentrations of carbon monoxide in air are commonly measured and expressed is one "part," or a certain number of "parts," of this gas mixed with 10,000 times as much air. A "part" is a hundredth of one per cent, or one ten thousandth of an atmosphere. A man at rest breathes about 8 liters, or 8,000 cc. of air per minute, of which about 6 liters reach his lungs, or 60 liters in 10 minutes. Let us suppose that the air in a street of heavy traffic contains, as it often does, one part of carbon monoxide, or 6 cc. in 60 liters, and that, while a man is breathing it, all of this 6 cc. is absorbed. His blood would then become saturated at the rate of one per cent every 10 minutes. If the air in a garage contains 10 parts of carbon monoxide, as it sometimes does, the rate of absorption would be ten times as rapid. If the man walks at a moderate pace and doubles his volume of breathing, or if while at work in a garage he increases the volume of his breathing four fold, or more, the rate of absorption will be correspondingly increased. Evidently the concentration of the gas, the duration of exposure and the volume of breathing are all factors in determining the amount absorbed. But a short exposure to a low concentration is harmless; for a man cannot absorb more than he inhales.

When a man begins breathing any moderate concentration of carbon monoxide mixed with air, absorption occurs at very

nearly such rates, but only at first. Then the rate becomes slower. Even if the exposure is prolonged, carbon monoxide merely displaces oxygen from the blood up to a point of equilibrium depending upon the relative amounts, or mass actions, of the carbon monoxide and oxygen in the air breathed and upon the intensity of the affinities of the two gases for hemoglobin. If thereafter the tension of oxygen is high enough and that of carbon monoxide is low, or absent as in pure air, oxygen can likewise displace carbon monoxide and thus completely restore the oxygen carrying power of the hemoglobin. The blood is neither directly changed nor injured by the process.

Hemoglobin attracts carbon monoxide about 300 times as strongly as it does oxygen. But the reaction is reversible. This means that if a sample of blood is shaken in a bottle in an atmosphere containing 300 times as much oxygen as carbon monoxide, the hemoglobin will be equally divided between the two gases: half combined with oxygen and half with carbon monoxide, for $300 \times 1 = 1 \times 300$. If that atmosphere is then replaced with another containing only 150 times as much oxygen as carbon monoxide—since 1×300 is twice as great a force as 150×1 —twice as much of the hemoglobin will be combined with carbon monoxide as with oxygen: in other words, the blood will be two-thirds saturated with the monoxide. And if the atmosphere is again changed to one of pure oxygen, or even air with no carbon monoxide, the result will be that all the carbon monoxide will be displaced, and the hemoglobin will be again combined with oxygen.

The same distribution of hemoglobin between oxygen and carbon monoxide according to the products of their tensions and affinities occurs in the blood in the lungs. Thus, if PO_2 and PCO are the tensions, or partial pressures, of oxygen and carbon

monoxide and HbO_2 and HbCO are the amounts of oxyhemoglobin and carbon monoxide hemoglobin in the blood, the relations are expressed by the formula:

$$\frac{\text{PO}_2 \times 1}{\text{PCO} \times 300} = \frac{\text{HbO}_2}{\text{HbCO}}$$

$$\frac{\text{PCO} \times 300}{\text{PO}_2 + (\text{PCO} \times 300)} \times 100 = \text{Percentage HbCO}$$

As a specific example: if there are 1500 parts of oxygen and 2 of carbon monoxide, the formula works out to:

$$\frac{2 \times 300}{1500 + (2 \times 300)} = 0.285$$

or 28.5 per cent saturation with carbon monoxide.

Air in the lungs contains about 15 per cent of oxygen, or 1500 parts in ten thousand. (It is actually somewhat less than 15 per cent. The affinity of hemoglobin for carbon monoxide may also be somewhat less, or more, than 300 times that for oxygen. We are here using round numbers merely to illustrate the principle without attempting mathematical precision.) On this basis we may calculate the equilibrium percentages of carbon monoxide in the blood for any concentration of carbon monoxide in the air; and from such data we may obtain the carbon monoxide dissociation curve of the blood: an expression of the fundamental relations established by Haldane.

This curve indicates that, if air containing two parts of carbon monoxide in 10,000 is breathed for a time long enough to attain equilibrium, the blood should become about 28 per cent saturated, which will induce a headache. With 4 parts it will ultimately become 44 per cent saturated, which will make a man unsteady on his feet, insensitive to pain and indifferent to danger.

With 6 parts, 58 per cent saturated, which may render him unable to stand. With 10 parts, 66 per cent saturated, which will render him unconscious and totally helpless. And with 15 parts, 75 per cent saturated, which may kill him. But it is to be noted that these figures apply only to equilibrium after prolonged exposure.

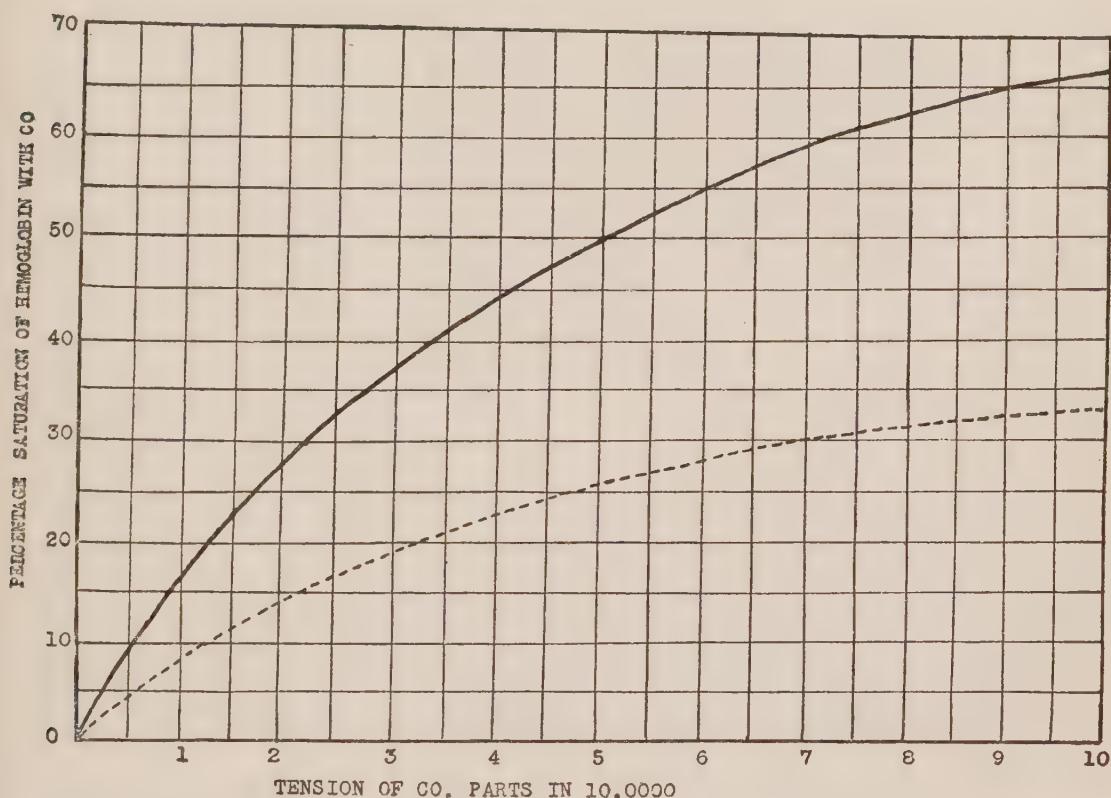


FIG. 6. Carbon monoxide equilibrium curve of blood, solid line, after prolonged exposures, as determined by Haldane; and curve for maximum degrees of saturation attainable in one hour during rest, as determined by Henderson and Haggard, broken line.

As the mechanics in a garage often work for a time in atmospheres containing considerable amounts of carbon monoxide, the question of practical importance is: How long a time in any particular atmosphere would be required to attain any particular percentage of saturation? What is the law defining the rate of

absorption? The formula given above indicates that a man breathing a certain number of parts of carbon monoxide would ultimately become saturated to a certain percentage expressing the equilibrium of oxygen and carbon monoxide in the blood. But to attain such a condition of equilibrium many hours would be required; indeed, the time is indeterminate.

The problem is somewhat like that involved in measuring the rate of radiation and decay in radium, which is also indeterminate; and we used the same general plan in solving it. We determined experimentally the length of time required for the blood to become combined up to half the equilibrium percentage for each particular concentration of carbon monoxide in the air breathed. And for all concentrations up to ten parts this period proved to be not less than one hour. The rule of safety thus determined is then that, if the air contains such an amount of carbon monoxide that the blood in full equilibrium with it would be combined with carbon monoxide to the degree shown by a point on the curve in figure 6, a man at rest may breathe that air for one hour before his blood will have taken up more than half the equilibrium amount; and generally the amount is less. The conditions that led us to work out this rule were as follows.

STANDARDS FOR VENTILATION OF TUNNELS AND GARAGES

When, in 1920, it was decided to construct tunnels for motor cars under the Hudson River at New York City, the standard of ventilation was one of the points upon which the late Clifford M. Holland, the able Chief Engineer for the New York and New Jersey Tunnel Commissions, desired precise information. The problem involved several features. One feature required a determination of the amount of carbon monoxide produced by

passenger cars and trucks of various sizes and power; and this part of the investigation was referred to A. C. Fieldner and his associates in the United States Bureau of Mines. On the basis of extensive investigation, they found that, in order to obtain rapid acceleration, carburetors are commonly adjusted to afford a rich mixture of gasoline in air. Consequently the combustion is so incomplete that one third of the fuel value of the gasoline is wasted, and the exhaust gas contains from five to nine per cent of carbon monoxide. The richer the mixture of gasoline and air to which the carburetor is set, the greater the acceleration of the motor in traffic and on hills, the less the mileage per gallon, and the higher the percentage of carbon monoxide in the exhaust gas. Roughly, 50 to 70 cubic feet of carbon monoxide (at 65°F.), are produced for each gallon of gasoline; and a car with the engine merely idling may produce a cubic foot of carbon monoxide per minute.

From such data Fieldner and his associates figured the amount of carbon monoxide that the average car or truck would discharge into the air of the tunnels. In addition the data permit one to figure the conditions in garages, and particularly to account for the fatalities in private garages. In a one car garage of such dimensions as 10 x 10 x 20 feet, or 2000 cubic feet, with doors closed, one cubic foot of carbon monoxide per minute produced by the motor would add five parts of carbon monoxide per minute to the air; or 50 parts in 10 minutes. In such an atmosphere of increasing carbon monoxide concentration the rule of absorption given in the previous section indicates that a man would be rendered helpless in 10 or 15 minutes, and that if the engine continues to run and he is not rescued, he would be dead in 30 or 40 minutes: long before the decrease of oxygen in the air would stop the motor.

The companion problem was to determine the concentration of carbon monoxide that might be breathed without ill effect by motorists during the time of passage through the tunnel and by traffic officers stationed in the tunnel. This problem was assigned to Haggard and me and we determined to solve it, not only for the tunnels, but for all conditions whatsoever. To this end we first carried out a series of 30 experiments upon ourselves and others of the investigative staff, 9 men and 1 woman, in which we spent an hour each time in an airtight chamber of 6

TABLE V
Summarizing experiments on men in six cubic meter gassing chamber

NUMBER OF EXPERIMENTS	PARTS CO IN 10,000 OF AIR BREATHED	CORRESPONDING EQUILIBRIUM VALUE OF THE BLOOD IN PERCENTAGE SATURATION	OBSERVED SATURATION IN THE BLOOD AFTER 1 HOUR		HEADACHES AND OTHER SYMPTOMS
			Minimum	Maximum	
2	2	28	11	12	None
3	3	37	10	14	None
11	4	44	14	22	None
9	6	55	18	26	None in 7; slight in 2
4	8	62	26	32	Marked in all 4
1	10	67	38	—	Severe

cubic meters into which measured amounts of carbon monoxide were introduced. The data so obtained are summarized in table V.

At the end of each test a sample of the subject's blood was analyzed by the carmine titration method, and a sample of his alveolar air by means of an iodine pentoxide train. The pulse and respiration were determined, and were found to be unaffected by one hour in concentrations of carbon monoxide below 5 parts but to be increased, particularly on any exertion, by higher con-

centrations. The Romberg test, the ability to stand erect with the eyes closed without wavering, was also used; and in most cases it indicated a distinct loss of balance after an hour in 8 or 10 parts of carbon monoxide.

After none of the tests in which the subjects spent an hour in four parts of carbon monoxide or less were there any appreciable effects. After some of those in 6 parts there was a feeling of lassitude. With 8 parts there was decided discomfort for some hours, although not enough to prevent efficient work in the laboratory or at the desk. After an hour in the chamber with 10 parts, with some exercise in the form of "standing-walking" or "standing-running," by lifting the feet as in walking or running, but without progress, even an unusually resistant subject (Y. H.) was quite miserable and averse to work for five or six hours and could still feel the effects after twelve hours.

Of all signs and tests the headache proved to be the most definite: a headache typical of oxygen deficiency alike from carbon monoxide and in mountain sickness. It is a distinctly localized pain, usually frontal, throbbing, intensified by lying down, or by exertion. It is frequently accompanied by nausea and sometimes by vomiting. It is due to congestion and edema of the brain. It develops gradually after the asphyxial conditions are ended and may last for 24 hours or more. The mind is not clear, except with an effort. The temper is easily upset, as in alcoholic intoxication, and the judgment may be bad.

These observations were next confirmed upon a group of 16 medical students who volunteered, as well as upon the members of the investigative staff, in a large chamber, 30 feet square, and of a capacity of 12,000 cubic feet. In this chamber a Model T Ford car was so installed that the rear wheels operated two large fans. The engine of the car ran with a fair load; and the power

was expended through the fans in mixing the air to a practically uniform concentration of carbon monoxide in all parts of the chamber. The engine discharged a total of about 25 cubic feet of exhaust gas with an average of 6 per cent of carbon monoxide, or 1.5 cubic feet per minute. The car was old and had had rough treatment; and the engine was somewhat irregular in action. The exhaust gas was, therefore, contaminated with rather more than the usual amount of gasoline, oil and soot, and other substances in addition to water vapor, carbon monoxide, and carbon dioxide. The experimental conditions were, in fact, quite realistic.

From 12 to 20 persons participated in each test. In all of those tests in which the concentrations of carbon monoxide in the chamber ranged from 2 to 5 parts per 10,000 the effects were negligible. But in a final large scale test, in which 17 men and 1 woman participated, analysis showed an average of 9 parts of carbon monoxide in 10,000 of air throughout the hour that they were exposed. In this test the amount of carbon monoxide absorbed and the subsequent effects were increased by the fact that a number of the participants, who had lost their fear of carbon monoxide in earlier tests, indulged in some rather vigorous games. As a result, their blood was found to have become from 27 to 37 per cent saturated, average 31. They, one and all, reported essentially the same effects: "Dizziness, headache and nausea. Throbbing headache and lethargy for 24 hours. Short period of dizziness. Severe headache for 9 hours, for 6 hours, 20 hours, 8 hours, 7 hours and 48 hours;" and in two cases "headache and vomiting." It was noteworthy that in most cases these ill effects set in after the hour in the chamber was ended, and increased in intensity for some time thereafter.

Upon the observations in the small and large chambers is based the rule of safety presented in the previous section: namely, that up to 10 parts of carbon monoxide in the air breathed, an hour is the minimum time in which the blood of a man at rest may reach half the equilibrium amount. For practical purposes the whole matter may be summed up in four equations in which the time is given in hours, the concentration of carbon monoxide in parts per 10,000 of air, and the intensity of the physiological effects in the figures 3, 6, 9 and 15. The physiological effects of all concentrations and times, not exceeding a few hours, may be defined as in table VI.

TABLE VI

Showing the relations of duration of exposure and concentration of carbon monoxide to severity of effects

1—Time × concentration =	3—no perceptible effect
2—Time × concentration =	6—a just perceptible effect
3—Time × concentration =	9—headache and nausea
4—Time × concentration =	15—dangerous

Physical exertion and increased volume of breathing will reduce the figure in the first equation from 3 to 2, or 1, or even less, and will affect the other equations correspondingly.

These standards are in essential agreement with those which Haldane had derived from his examination of conditions in the London underground railroads. Our proposal that in the Holland Tunnels the ventilation should be sufficient to keep the concentration of carbon monoxide at or below 4 parts in 10,000 of air, was adopted—in fact, it has since been adopted in a number of other tunnels in Europe and elsewhere.

Finally, when our work on men was done, and Fieldner's studies on motor cars at the Bureau of Mines Experiment Sta-

tion in Pittsburgh were completed, a combined experiment was arranged. It took place on an elliptical motor road constructed far back in the Bureau of Mines experimental coal mine. There were, as I remember it, 10 Model T Ford cars driven in low gear in a procession round and round that subterranean road for 20 minutes. I elected to drive one of the cars; and I soon realized that, instead of keeping the carbon monoxide down to four "parts," our proposed standard, the ventilation actually had allowed a pollution of the air by 4 or 5 times as much exhaust gas as we had intended. I realized also that I had absorbed enough of the gas to render me unconscious on even slight exertion; also that I had a reputation as a "smoke eater" to maintain before a lot of chemists and engineers. Accordingly, at the end of the run, I alighted from my car with all the dignity that I could command, and walked very slowly out into fresh air. There I sat down and watched while my colleagues of the Chemical and Engineering Sections, who had arranged the ventilation in that test, were carried out and laid unconscious on the grass. They had been exposed to rather less of the gas than I; but, as they had less experience, they had also been less careful to avoid exertion. (I chaffed them later on their relatively low capacity to "eat smoke.")

However, no harm was done, beyond a few highly instructive headaches, of which I had one. Later tests, in which the ventilation was sufficient to keep the gas down to our recommended standard, went off without even a headache. Many millions of motorists have since been spared a headache because of our experience. By contrast, in another vehicular tunnel elsewhere, opened at about the same time, in which a block of traffic occurred before efficient ventilation was installed, a large number of persons were removed in a state of asphyxial coma.

INDIVIDUAL DIFFERENCES

As part of our investigation, A. L. Prince examined the blood of a number of patients with various diseases and compared them with the blood of healthy persons, in order to determine whether any considerable variation in the affinity of hemoglobin for carbon monoxide occurs. No significant differences were found. Some persons develop headache more readily than others, or faint more easily. But the more serious effects of the anoxemia occur in all persons at about the same percentage of saturation with carbon monoxide. The one significant difference in the rate at which asphyxia develops is due to differences in the volume of breathing. This is the reason that when an entire family is asphyxiated by carbon monoxide from a leaking stove pipe or a gas water heater, the children generally die first. Their higher rate of metabolism and relatively greater volume of breathing induce a correspondingly more rapid absorption of the gas. For the same reason small animals, such as mice and canaries, are used as indicators of the presence of dangerous amounts of carbon monoxide in mines after fires or explosions. As they breathe 20 or 30 times as large a volume of air for their mass as does a man, they are correspondingly more quickly overcome. The complete reversibility of the reaction between carbon monoxide and hemoglobin is evidenced by the fact that mice and canaries can be repeatedly rendered unconscious and as often revived, without subsequent ill effects. The harm done by carbon monoxide is not due to any direct toxicity; but wholly to oxygen want and is proportionate to the length of time that the tissues, particularly the brain, suffer from the oxygen want.

AFTER-EFFECTS OF ASPHYXIATION

After a man leaves a garage, or repair shop, where his blood may have become from 10 to 30 per cent saturated with carbon

monoxide, headache and nausea may grow upon him for several hours. Acute cases of asphyxia, due to severe and prolonged gassing, may remain in coma for hours or days. The natural inference from both classes of cases is that so long as the headache or the coma lasts the blood must still contain carbon monoxide.

Such is, however, by no means the case. Long before the headache ends, or consciousness returns, the oxygen of the air has displaced all the carbon monoxide from the blood. In the experiments in both the small and large chambers examination of the blood for several hours after the gassing showed that from 30 to 50 per cent of the amount in the blood was eliminated each hour, depending upon the bodily activity and volume of air breathed. The headache lasted much longer.

Similarly in the cases that, after acute asphyxia, remain in coma until death a day or two later the amount of carbon monoxide in the blood decreases hour by hour. In my early experiences 30 years ago, I was puzzled by finding that the cases of asphyxiation, induced by sleeping in a room with an open or leaking gas burner, had generally eliminated the greater part of the carbon monoxide from their blood within a few hours. In six successive cases in which I examined the blood two or three hours after the patient had been removed to fresh air, there were only two in which the degree of saturation was still above 20 per cent; and four or five hours after removal from the gas, the blood contained only a trace of carbon monoxide. Yet all, judging from their coma when rescued, had certainly been saturated to at least 60 per cent; and four of them died in 24 to 60 hours after the asphyxiation. One recovered completely; and another survived but with serious nervous impairment.

After Claude Bernard discovered that the effects of carbon monoxide are due to its combination with hemoglobin, it was

long supposed that the compound so formed was permanent. Accordingly the victims of gases were bled and transfused. And this treatment has only in recent years been given up. How useless it was is illustrated by the following cases:

Three men, all members of a Filipino band that visited this country at the time of President Taft's inauguration (1909) were overcome by illuminating gas while sleeping in a room together. All three were of the same age, weight and physique. They were as much alike as three guinea pigs and afforded as ideal an experiment as could possibly be planned. They were taken to the hospital and during the following day, at my suggestion, one was treated by bleeding and injection of saline saturated with oxygen. A second received a transfusion of blood from an unpoisoned member of the band. It was done in the afternoon, after nearly all the carbon monoxide had been eliminated from his own blood. For the third man nothing was done beyond ordinary nursing care. The first two died in the course of two or three days. The third survived; but three weeks later he was still scarcely able to answer a question as to his name or home.

OTHER TOXIC SUBSTANCES

In the course of our investigation for the Tunnel Commissions we carried out a number of fatal and near fatal asphyxiations on dogs. Pure carbon monoxide was mixed with air in a small chamber to a concentration of 20 or 30 parts. In this atmosphere the animals became unconscious with no more apparent discomfort than if anesthetized with ether. The blood, at the point of death, contained in five cases: 87, 82, 84, 79, and 88 per cent of saturation: average, 84 per cent.

When illuminating gas, containing 25 per cent carbon monoxide, was used in essentially the same dilution of the monoxide

in the chamber, the animals exhibited symptoms of discomfort, including vomiting, before becoming unconscious. At death the blood of four dogs contained 74, 67, 76, 71 per cent of carbon monoxide: average, 72 per cent.

When the exhaust gas of a car using coal distillate—a mixture of benzol, toluol, and naphtha—was used, the percentages of carbon monoxide in the blood of two dogs at death were 60 and 62. The blood had the brownish tinge characteristic of benzol poisoning.

Evidently in the last two groups of cases, while carbon monoxide was the principal cause of death, other constituents of the mixture of gases were also toxic. On the other hand, when gasoline is used the small amount of its vapor in the exhaust gas does not add appreciably to the toxicity of the carbon monoxide. Haggard found that at least 80 to 100 parts of gasoline vapor in 10,000 of air were required to induce convulsions in dogs and 250 parts to cause death.

THE FALLACY OF CHRONIC POISONING

Carbon monoxide is not a cumulative poison. There is, therefore, no such condition as the expression "chronic carbon monoxide poisoning" would imply. In pure air and with a sufficient volume of breathing this gas is readily ventilated out of the blood. Unlike lead or silica dust, it cannot accumulate in the body progressively over long periods. Repeated exposures, as in garage mechanics, blast furnace workers and cooks may temporarily, but only temporarily, impair health. More often a compensatory polycythemia develops, like that in acclimatization to altitude.

After severe asphyxiation, followed by prolonged coma, the victim generally dies within 36 hours without regaining con-

sciousness; or else he recovers completely in a few days. The belief in "chronic carbon monoxide poisoning" arises from the fact that in occasional cases a prolonged asphyxiation damages the brain too deeply for complete restoration, but not quite enough to kill. The patient then survives with impaired mind, particularly loss of memory, and paralysis or sensory defects. These sequelae are due, not to retention of carbon monoxide, but to degeneration of the nerve centers. The determining factor in their production is the length of time that the tissues have been subjected to oxygen want.

Claims of impaired health from exposure to carbon monoxide are now common as the basis of law suits. In the majority of cases these claims are unjustified. They should not be accepted as valid unless all of three conditions can be established: (1) At least a 50 per cent saturation of the blood, or a concentration of carbon monoxide in the air sufficient to induce at least 50 per cent saturation. (2) An exposure of three to ten or more hours. And (3) continuous complete unconsciousness lasting for six to twenty-four or more hours after return to fresh air. Short of conditions of such severity recovery is practically always complete.

CARBON MONOXIDE ACTS ONLY THROUGH HEMOGLOBIN

Carbon monoxide has no toxic quality, other than that of combining with hemoglobin. In the tissues there is indeed another iron containing substance—the catalyst cytochrome—which plays a part in the utilization of oxygen by the cells. Cyanides kill by combining with cytochrome. But the affinity of cytochrome for carbon monoxide is so low that a concentration of carbon monoxide sufficient to induce a fatal degree of saturation of hemoglobin would have no appreciable effect on cytochrome.

Ignorance of this fact led to the introduction, for a time, of methylene blue as a counter-asphyxiant. Although this substance has some oxidizing power in the tissues, it also converts hemoglobin into methemoglobin, and thereby further decreases the oxygen capacity of the blood. Methylene blue and some other oxidizing agents are of value in the treatment of cyanide poisoning; for the methemoglobin which they produce in the blood combines with cyanide. But they are harmful in carbon monoxide asphyxia.

Haldane found that such animals as insects which have no hemoglobin in their blood, but do have cytochrome in their tissues, are entirely unaffected by carbon monoxide; and that a mouse that has been prostrated with carbon monoxide becomes active again under a pressure of oxygen sufficient to cause a considerable amount of that gas to be carried in simple solution in the blood. Furthermore Haggard showed that nerve cells taken aseptically from the brain of a chick grow quite as well in 79 per cent of carbon monoxide and 21 per cent of oxygen, as they do in air: thus demonstrating that carbon monoxide is no more poisonous for nerve cells than is the 79 per cent of nitrogen in the air.

The latest and most complete evidence on the purely anoxic, but otherwise non-toxic effects of carbon monoxide is afforded by the work of Yant, Sayres, and their associates in the Bureau of Mines and the Public Health Service. (The most complete review of this entire subject is also that of Sayres with Davenport.) These investigators have carried out two parallel series of experiments on asphyxia: one by means of carbon monoxide, and the other by means of atmospheres so low in oxygen that the oxygen content of the blood was decreased as much as in the experiments with carbon monoxide. The changes in the blood

were the same in the two series: increased blood sugar and non-protein nitrogen, decreased bicarbonates, etc. And as these effects were found to be reversible, when the subjects (dogs) were resuscitated by inhalation of oxygen or oxygen and carbon dioxide, they are not the cause of postasphyxial deaths. The brains, both of the animals that died during and after asphyxiation, and of those that survived until killed at various periods after the gassing, were examined microscopically, and showed the same kinds and degrees of degeneration in the cerebral cortex and basal ganglia in both series.

EDEMA OF THE BRAIN

For us the headache of carbon monoxide and other forms of anoxemia had acquired a strong personal interest. It is the headache that is almost the trade sickness of garage and repair shop workers. For other investigators, particularly Stanley Cobb, F. F. Smith, and H. S. Forbes, the interest of this headache lay rather in its neurological aspects; for they had observed a marked increase of pressure in the cerebro-spinal fluid in cases of asphyxia, and they wished to know the cause. To this end we gladly contributed our experience in the technique of gassing.

The subjects of our experiments were cats and young dogs; and in order to avoid the complicating feature of ordinary anesthesia, the animals were anesthetized with carbon monoxide, then tracheotomized and kept in coma for several hours. As an excess of gas readily leads to collapse in small animals, some of them had repeatedly to be revived from imminent death.

As soon as they were unconscious, a hole was trephined through the skull, through which the surface of the brain could be watched. As a rule, no considerable effect of the asphyxia was noted for an hour or more, other than increasing vascular

congestion. Then the brain gradually pressed up into the hole in the skull, and in extreme cases even squeezed out through it in a small bulbous mass, that continued to protrude further even after the asphyxia ended. Indeed, the edematous swelling of the brain followed, rather than accompanied, the period of asphyxia.

Intravenous injection of a strong saline solution caused a fairly rapid shrinkage of the brain back to its normal volume, as Weed and McKibben had previously observed. The significance of this observation lies in the fact that some headaches are relieved by withdrawal of water from the body by a saline cathartic.

While we were doing these experiments, it occurred to us to try also to imitate those cases of asphyxiation in men which leave the victims with permanent nervous or mental impairment. And, with care, we succeeded in subjecting a dog to such prolonged sub-lethal asphyxiation that, after the gas had been eliminated, the animal remained completely mindless. For as long as it lived, it was a total idiot.

Chapter VII

RESUSCITATION FROM CARBON MONOXIDE ASPHYXIA

IN 1881 the International Encyclopedia of Surgery contained descriptions of carbon monoxide and carbon dioxide—called “carbonic oxide” and “carbonic anhydride”—which record what was then known, or believed, regarding these gases:

“Carbonic oxide, CO. Sp. gr. 0.967. A transparent, colorless, inflammable, almost odorless gas. It is ordinarily produced by the combustion of coal with a limited supply of oxygen. Its action is exceedingly energetic. The presence of one tenth of one per cent of this gas is sufficient to destroy a bird, and two or three tenths of one per cent will kill a dog. It forms a permanent combination with the hemoglobin of the blood, expelling oxygen, and producing insensibility and death by asphyxia. Resuscitation is rendered almost impossible by the stability of the compound which it forms with hemoglobin.

“Carbonic anhydride, CO_2 , carbonic acid gas. Sp. gr. 1.529. A colorless, transparent gas, with a slightly acid taste and smell. The gas causes speedy death by asphyxia if inhaled without dilution. If it exceeds three or four per cent of the air that is breathed, giddiness, dyspnoea, muscular weakness, and feeble and rapid movements of the heart appear. Any considerable increase of the gas intensifies these phenomena and will destroy life, even though a considerable amount of air be present. Death results partly through exclusion of oxygen from the blood, and partly from the directly anaesthetico-toxic action of the substance upon the nervous tissue. A few surgeons have attempted to combine the action of carbonic acid with the vapor

of ether, by causing the patient to respire from a closed receiver containing the vapor, thus consuming his own breath until rendered insensible by its carbonic acid mingled with ether. This practice cannot be too strongly condemned."

While some of these statements are correct, we now know some of the others to be the exact opposite of the truth. Carbon monoxide does not "form a permanent combination with the hemoglobin of the blood"; and resuscitation is not thereby "rendered almost impossible." On the contrary, if the victim has not already reached the stage of fibrillation of the heart, which Haggard found to be the final and fatal event in asphyxiation, he is now generally resuscitated. In anesthesia the use of rebreathing is now recognized as beneficial. Much more than 3 or 4 per cent of carbon dioxide is administered after surgical operations. It has no "anesthetico-toxic action." On the contrary it hastens elimination of the anesthetic, as first shown by White, and prevents atelectasis and pneumonia. It is also effective in controlling postoperative hiccup, as first demonstrated by Sword.

Yet the descriptions above quoted expressed general medical opinion, not only in 1881, but in 1921; and similar statements are occasionally made even now. The opinion was that the victims of asphyxiation lived or died as fate might decide; for apart from transfusion of blood it was believed that "resuscitation is almost impossible." Even as late as 15 years ago there was still justification for a well-informed and conscientious doctor that I knew who, when he received an early call to a case of asphyxiation, telephoned back: "Open the windows and I will be up after breakfast." And indeed his patient, so treated, had a better chance to recover than if he had received some hypodermic injection: the treatment then common, and as valueless then as now.

Before automobiles became common, asphyxiation by carbon monoxide was generally induced by city gas: it was the favorite means of suicide. Defective gas appliances were common and accidental asphyxiations were correspondingly frequent. Such cases still occur; for within the past year we have examined a gas water heater that had caused a death; and we found that it rendered the atmosphere of a small room deadly in half an hour. Even if supplied with natural gas—methane, which is itself non-poisonous—the flame, striking the cold water pipes, would produce carbon monoxide. Improvements in domestic gas appliances and stricter supervision have somewhat decreased the cases of accidental asphyxiation in homes. In many cities and towns would-be suicides have so often been resuscitated that intentional self-asphyxiation by city gas is now less common than formerly. Yet there are still many thousands of cases of all types of asphyxiation; and of these a large percentage are now not only resuscitated, but are completely restored to health by inhalation of carbon dioxide and oxygen. If this treatment is administered in time, it not only saves life; it also prevents all the harmful after-effects of asphyxiation. The benefits are not merely the stimulation of respiration and accelerated elimination of carbon monoxide. The restoration of a full circulation of the blood and the recall of alkali in the blood are equally important for complete and rapid recovery.

POST-ASPHYXIAL DEPRESSION OF BREATHING

Our investigations for the Tunnel Commissions had confirmed Haldane's estimate of the rate at which carbon monoxide is eliminated from the blood after such degrees of saturation as an experimenter may safely try on himself or his associates and students. After a short exposure, inducing only 40 per cent, or even 50 per cent saturation of the blood, respiration is not

much depressed; elimination begins as soon as the subject comes into fresh air, and proceeds at such a rate that approximately half of the gas has been eliminated within an hour.

In dogs, after the absorption of corresponding amounts of carbon monoxide, an even more rapid elimination begins at once. The determining conditions for the elimination are the volume of the pulmonary ventilation and the relative tensions of oxygen and carbon monoxide in the lungs, during the time that the monoxide is being washed out.

Why then was the treatment of cases of asphyxiation with oxygen so ineffective, as it had proved to be? One reason is that, until proper inhalators were introduced a few years ago, oxygen was generally administered through an inverted funnel held so far above the face that little of the gas reached even the nose and mouth of the patient. A second reason was more fundamental: respiration in profoundly asphyxiated persons is so much depressed that, if oxygen alone is administered, it is inadequately inhaled. And a third reason is that, because of the extreme acapnia and acute anoxemia in an asphyxial patient, the first few breaths of pure oxygen may further depress respiration, or stop it altogether. This is the effect that Mosso termed "oxygen apnea," and that Marshall has recently observed when oxygen is administered to animals in barbiturate narcosis. It may kill.

In our experiments no serious depression of respiration occurred in any of the men or animals that had absorbed only moderate amounts of carbon monoxide—up to 40 per cent saturation. But in those of our experiments in which dogs were brought into coma, with 60 or 70 per cent of saturation, there was often marked over-breathing during the development of asphyxiation, and a correspondingly marked depression of breathing after the

animals were removed to fresh air, or were treated with oxygen. Their respiration became so feeble that, although their bodies were now surrounded by fresh air, their brains were still subjected to oxygen want to almost as great an extent as when they were still in the gassing chamber.

That anoxemia induces over-breathing—probably through a production of hyperpneia—and that over-breathing induces acapnia, acarbia, and finally depression of breathing were shown by such experiments as the following: A dog was gassed with 25 parts (0.25 per cent) of carbon monoxide—in city gas mixed with air—administered by means of a mask and valves. The volume of breathing increased steadily from 4.5 liters at the beginning to 12 liters per minute at the end of $3\frac{1}{2}$ hours. The unconscious animal, about 60 per cent saturated, was then allowed to breathe fresh air. Its volume of breathing gradually decreased and an hour later we noted: "Gasps, apnea, death." During the gassing, as the carbon monoxide content of the blood increased, the carbon dioxide diminished. The carbon dioxide content of the arterial blood before gassing was 38 volumes per cent; but only 18 volumes per cent when the animal was removed to fresh air. The blood alkali (determined at 40 mm. pressure of carbon dioxide) fell correspondingly from 38 to 25 showing a typical state of acapnia and acarbia.

In another case the initial volume of breathing was 6 liters per minute, but after breathing 17 parts of carbon monoxide for 6 hours, it was 21 liters per minute. The arterial carbon dioxide and the blood alkali were initially 41 and 40, and after 6 hours, 17 and 26. After removal to fresh air respiration was greatly depressed. In a similar experiment an intravenous injection of sodium bicarbonate was followed by tetany, failure of respiration and death.

In these and all similar experiments the pH of the blood during the hyperpneic period of gassing was high. During the subsequent period in air, when respiration was weak or failing, the pH was, of course, low. This was not, however, an indication of acid intoxication. It was rather the effect of the sub-normal respiration, and tended to recall alkali to the blood.

In one experiment the vagi were cut under cocaine and the animal was then made to breathe 50 parts of carbon monoxide in 10,000 of air until it died after 75 minutes. In this case no increase in the volume of breathing occurred and no decrease of the blood alkali. We inferred (1) that, sometimes at least, anoxemia increases the excitability of the respiratory center through the vagal endings in the lungs, as it has since been shown to do through the sinus caroticus; and (2) that in the absence of over-ventilation and acapnia, no decrease of blood alkali is induced by oxygen deficiency. The first of these inferences has not been found to hold in other dogs, either by other investigators or by us. But the second, and more important inference—namely, that, without acapnia, anoxemia does not induce acarbia—is in my opinion correct.

THE ELIMINATION OF CARBON MONOXIDE

A point of extreme practical importance developed from these experiments: a point that we and all others had previously overlooked. The experiments showed that asphyxiation does not end when a man or animal is removed from a gassing chamber to fresh air. So long as the depression of respiration lasts, the blood retains the greater part of all the carbon monoxide that it has absorbed; and the asphyxiation continues. To terminate the anoxemia and prevent damage to the brain, it is essential to eliminate the carbon monoxide from the blood as rapidly as

possible. There is only one way in which this can be accomplished: namely, by stimulating respiration to a greatly increased ventilation of the lungs. Recognizing this need, we realized for the first time why it is that in cases of profound asphyxia inhalation of oxygen alone may not prevent damage to the brain, and may even fail to save life. If it were not for the depression of respiration, oxygen alone would doubtless be—as some writers still insist it should be—effective as a means of rapid resuscitation.

At this time (1922) Haggard, Coburn and I had recently (1920) demonstrated the benefit of inhalation of carbon dioxide in patients after surgical operations, a benefit for which I had long contended. Respiration was thereby stimulated; the anesthetic was rapidly ventilated out of the blood; the circulation and heart action were improved; consciousness was soon recalled and nausea was lessened or prevented. We therefore now undertook a series of experiments in which we compared the rate of elimination of carbon monoxide in deeply asphyxiated dogs when treated in four different ways: (1) with air alone; (2) with oxygen alone; (3) with carbon dioxide in air; and (4) with carbon dioxide in oxygen.

In these experiments each dog was asphyxiated separately in a glass-walled chamber of about 0.7 cubic meter capacity into which enough city gas was introduced to produce an atmosphere of 30 to 40 parts (0.3 to 0.4 per cent) of carbon monoxide. At first the animal moved about restlessly; then it developed a stage of excitement like that under ether; then muscular weakness. The animal's hind legs relaxed, and it supported itself with widespread forelegs. Respiration became more and more vigorous, up to violent and prolonged hyperpnea. The animal then lay down, and thereafter made only an occasional feeble move-

ment. The breathing became of the Cheyne-Stokes type, and unconsciousness followed. After 5 or 10 minutes of complete unconsciousness the animal was removed from the chamber; a sample of blood was taken for analysis; and additional samples thereafter were taken at intervals, while one or another of the four treatments, above indicated, was administered.

Although these animals were asphyxiated by carbon monoxide, they were also affected by the other toxic substances in the city

TABLE VII

Showing rates of elimination of carbon monoxide under various treatments
Per cent HbCO

TIME, MINUTES						DOG	TREATMENT
0	20	40	60	80	120		
41	39	28	20	12	4	(A)	Breathed air only
62	58	55	45	33	16	(B)	Breathed air only
64	62	62	(apnea and death)			(C)	Breathed air only
58	55	50	33	12		(D)	Breathed oxygen
55	53	—	10			(E)	Breathed oxygen
49	36	8				(F)	Breathed air and 6.5% CO ₂
61	54	36	24	4		(G)	Breathed air and 6.5% CO ₂
55	15	2				(H)	Breathed oxygen and 10% CO ₂
60	55	28	4			(I)	Breathed oxygen and 10% CO ₂

gas. As shown in the preceding chapter, death occurs at about 65 per cent saturation when these substances are present with carbon monoxide; and only at 85 per cent saturation when they are not. But as these substances are powerful respiratory stimulants, the conclusions drawn from these experiments are not thereby invalidated. Indeed, the results indicate even more clearly than with a pure carbon monoxide asphyxia, that the depression of breathing after asphyxiation is partly due to the

excessive over-breathing and consequent acapnia, as well as to depression of the respiratory center by prolonged anoxemia. And not only respiration, but all the vital functions are depressed.

The rates of elimination of the carbon monoxide (CO) combined with the hemoglobin (Hb) of the blood under the various treatments administered, after the animals were removed from the gassing chamber are shown in table VII. The data in table VII are shown graphically also in figure 7. They demonstrate

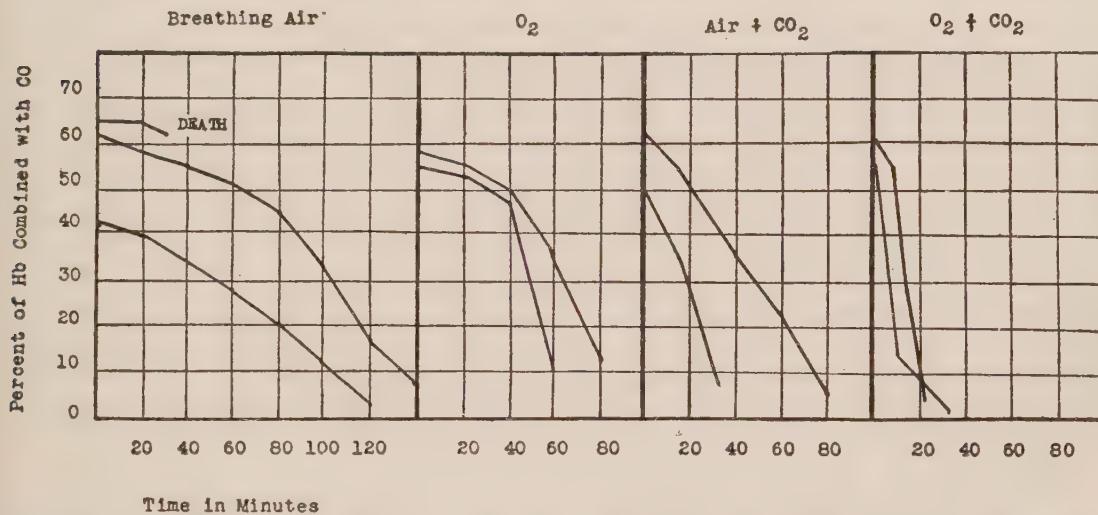


FIG. 7. Rate of elimination of carbon monoxide from the blood of dogs when breathing air, oxygen, carbon dioxide and air, and carbon dioxide and oxygen.

that the higher the percentage saturation of the blood with carbon monoxide, the greater the subsequent need for stimulation of respiration and other functions with carbon dioxide.

EXPERIMENTS ON MEN

In order to determine how far effects on men might correspond with those on animals, Haggard and I performed essentially similar experiments on ourselves and some of our associates. Although the concentrations of carbon monoxide in the air breathed were as high as for the dogs, the periods of exposure

were somewhat shorter, and the degrees of saturation less. Instead of city gas, the carbon monoxide was made from formic acid. In the therapeutic inhalations after the gassing, a mixture of 5 per cent carbon dioxide and 95 per cent oxygen was inhaled. We had found that higher percentages of carbon dioxide may induce a headache. This was a mistake in procedure; for, as we later learned, in some persons 5 per cent carbon dioxide is inadequate to stimulate respiration considerably. For the resuscitation of cases of severe asphyxiation, concentrations of 8 to 10 per cent of carbon dioxide in oxygen were later found to be much more effective.

The procedure was for the subject on three separate days to spend from thirty to forty minutes in a gassing chamber of 6 cubic meters capacity, the air of which contained about 20 parts (0.2 per cent) of carbon monoxide. At the end of this time the blood analyses revealed from 35 to 50 per cent of saturation. This is enough to render a man, who thereafter is untreated, severely ill with headache, nausea, vomiting and vertigo. A few hours in such an atmosphere would kill.

Immediately after the subject came out of the gassing chamber he lay down; and on two of the three days a therapeutic inhalation was administered to him for twenty-five or thirty minutes. Three comparative experiments were done on each of four subjects: (1) with inhalation of a mixture of carbon dioxide and oxygen, (2) with oxygen alone, and (3) merely with fresh air. In all of these experiments samples of blood were taken and analyzed by the tannic acid method of Sayers and Yant before gassing, immediately after gassing, and at fifteen minute intervals thereafter.

Protocols of experiments on Y. H., male aged 49, weight, 170 pounds (77 kg.):

(a) Gassed in 0.2 per cent carbon monoxide for thirty minutes, standing and moving during the gassing. Then he came out of the chamber, lay down, and inhaled oxygen and carbon dioxide for twenty-five minutes. The volume of breathing increased from 9 liters in the first minute to 15 liters in the second minute, 20 liters in the third, 30 liters in the fourth, and continued at about this volume throughout the inhalation. No discomfort was felt during the inhalation, but there was a slight headache afterward, otherwise the subject was well.

(b) Same subject, next day, similar experiment; but after gassing, inhaled oxygen alone. The volume of breathing during this inhalation was diminished to only 5 liters a minute—the normal for this subject was 7 or 8 liters and his respiration was distinctly irregular, almost of the Cheyne-Stokes type. For a time the heart action was also irregular. During the rest of the day the subject was irritable and tired, but not distinctly unwell.

(c) After a similar experiment on another day, the subject merely breathed fresh air. He was distinctly unwell with throbbing frontal headache for 12 hours.

The percentage saturations of the blood were as follows:

EXPERIMENT	BEFORE GASSING	AFTER GASSING, MINUTES			
		2	15	30	60
A	0	35	25	15	12
B	0	35	32	27	25
C	0	38	—	—	33

Protocols of experiments on H. W. H., male, aged 30, weight, 200 pounds (91 kg.). Gassed and treated as was the previous subject.

(a) After the gassing, the volume of breathing under inhalation of oxygen and carbon dioxide increased from 9 to 30 liters. No uncomfortable after-effects whatever.

(b) After the gassing, oxygen alone was administered. Respiration was at first subnormal, then about normal, 10 liters a minute. Headache developed with increasing intensity all day, with dyspnea on exertion, rather miserable.

(c) After a somewhat less intense gassing with no treatment other than

fresh air, this subject developed a frontal headache and malaise lasting all day and followed by a sleepless night.

The percentage saturations of the blood were as follows:

EXPERIMENT	BEFORE GASSING	AFTER GASSING, MINUTES			
		2	15	30	60
A	0	50	30	15	12
B	0	45	42	40	35
C	0	34	—	—	29

The other subjects afforded similar results with the exception of one who responded to 5 per cent carbon dioxide with only a slight increase of breathing, and was not much better after treatment with oxygen and carbon dioxide than with oxygen alone. Such cases indicate that in the treatment of severe carbon monoxide asphyxia the percentage of carbon dioxide should be at least 7; and that 10 is not generally, if ever, too much.

THE H. H. INHALATOR

At this point the H. H. inhalator comes into the story. An account of how that apparatus was developed for us by the Mine Safety Appliances Company will be given in the next chapter. Without that apparatus our treatment of asphyxia with carbon dioxide and oxygen would have remained unused; a mere laboratory product. In the H. H. inhalator we had, on the contrary, the essential means of administering that treatment effectively. All that was lacking was an opportunity to put the treatment to a large scale practical test. And thanks to Dr. C. K. Drinker, the American Gas Association, and the Consolidated Gas Company, this opportunity was now offered in the City of New York.

THE COMMISSION ON RESUSCITATION

Dr. Drinker was then acting as adviser in matters of sanitation to the American Gas Association. On his advice that Association authorized him to organize a Commission on Resuscitation, and appropriated a fund to cover the expenses of investigations done under the Commission. The membership was C. K. Drinker, chairman, W. B. Cannon, D. L. Edsall, L. J. Henderson, F. W. Peabody, W. K. Lewis, R. R. Sayers, C. B. Scott, H. W. Haggard and Y. Henderson. And the last two were appointed a sub-committee to try out the new inhalational method of resuscitation.

The City of New York afforded ideal conditions for such a test. The Consolidated Gas Company maintained five emergency auto trucks, each with three crews on eight hour shifts, on duty 24 hours a day. Within a few minutes from the time a case of asphyxiation was reported from anywhere in the city, one of these trucks and its crew were on the spot: usually even ahead of the hospital ambulance.

The treatment we had developed was not one for hospitals: not even for the emergency room and accident ward. To be fully effective, it must be administered at the earliest possible moment; for during even a short ride in the ambulance the asphyxiation would continue. A case that might have been saved, if treated in the home, might be beyond resuscitation by the time it reached the hospital; and the hospitals were not then equipped to treat asphyxia. Not the least of the difficulties that we had to overcome was to persuade the white-coated internes, who came on the ambulances from the hospitals, to keep their hypodermic syringes in their pockets, and leave the victims of asphyxiation to be treated by the rescue crews. Many cases,

which the internes then and later declared beyond help, have been successfully resuscitated by the men of these crews.

On each truck was placed an H. H. inhalator, and the men were instructed in its use; for it was really the members of these crews who were to decide on the efficiency of the carbon dioxide-oxygen treatment. They had seen hundreds of cases of asphyxiation and had treated them with the pulmotores with which the trucks had previously been equipped: the same pulmotores that another Commission, ten years earlier, had condemned, but which until then had continued to be used for lack of any more efficient treatment. It was the enthusiasm of the men of these rescue crews, when they found that with the new treatment cases were resuscitated that under the pulmotor had generally died, that won the day for carbon dioxide and oxygen, and the H. H. inhalator.

Acknowledgments and thanks are also due the Union Carbide and Carbon Company and the Linde Air Products Company for making and supplying all of the carbon dioxide and oxygen used in this test; to the Health Department of the City of New York and to Bellevue Hospital and its pathological department for efficient cooperation; to the Bureau of Mines for assigning Dr. Stuart Scott, then one of its medical staff, to aid us in collecting data; and above all, to the Mine Safety Appliances Company which placed these inhalators at the service of this investigation, and has done more than all other agencies to bring the inhalational treatment of asphyxia into the universal use that it has now (1937) attained.

LARGE SCALE PRACTICAL TEST

Even with all this cooperation, the difficulties of the investigation, inherent in the conditions under which asphyxia-

tions occur in a great city, proved to be very considerable. It is a trying task to wait for days, idle, knowing that a call may come at any minute of the day or night; then to go at top speed to one end of the city, only to find that the patient was dead when discovered; to rush back to the other end of the city to find a patient spontaneously recovered; and finally, to arrive late at a case which would have been ideal, if fully observed. But even in regard to such cases as that last mentioned, much of value was obtained. Each of the rescue crews was instructed to administer the oxygen and carbon dioxide inhalation as soon as the hospital ambulance arrived and permission was given by the physician. The amount of evidence regarding the effect of the inhalation so obtained from these physicians and the crews was considerable, in addition to that from cases which we ourselves observed.

An elaborate questionnaire was drawn up and mimeographed; and on it information on the following points was recorded: (1) previous medical history of the victim; (2) physical characteristics, age, weight, etc.; (3) suicide or accident; (4) size of the room, amount of gas and duration of asphyxia; (5) time elapsed before discovery of victim and application of measures for resuscitation (very important); (6) condition of patient at initiation of measures for resuscitation: respiration, pulse rate and force, and particularly a blood sample for analysis to determine the degree of saturation with carbon monoxide; (7) behavior of patient under treatment; (8) condition, physical and mental, and the content of carbon monoxide in the blood at the end of the treatment—usually from fifteen to twenty minutes; (9) condition of patient in all respects an hour or two later; (10) next day, and (11) subsequently.

OBSERVATIONS ON CASES OF POISONING BY CITY GAS

The outstanding facts established regarding the cases of city gas poisoning to which the oxygen and carbon dioxide inhalation was applied may be thus summarized: The treatment itself induced no ill effect in any case. The administration of a preliminary dose of 0.01 grain of atropin, which we had thought might be advisable, proved entirely unnecessary; for the heart was never adversely affected.

In every case the respiratory response to the inhaled carbon dioxide consisted in a rapid increase in the volume of breathing up to full and deep pulmonary ventilation. Some of the patients were barely breathing, the pulse also weak, before inhalation was begun. Breathing in some had even to be started by means of manual artificial respiration. All, however, in whom there was still life responded effectively, and none failed or sank under the inhalation. Frequently the volume of breathing increased within five minutes to the full 30 liters of oxygen and carbon dioxide which is the maximum that the inhalator will supply, and beyond which a supplemental volume of atmospheric air is automatically drawn in. In most cases the other vital functions improved correspondingly.

Most significant was the extremely rapid reduction of carbon monoxide in the blood; the concentration falling from asphyxial amounts to practically negligible percentage saturations (10 or 15) in fifteen or twenty minutes. In several cases the blood was virtually free from carbon monoxide at the end of the 30 or 40 minute inhalation: a result distinctly better even than had been attained in the experiments on men and animals in the laboratory.

In several of the cases of profound asphyxiation, the patients had recovered full consciousness within a half hour after the initiation of inhalation. Only one patient failed to return to

consciousness within an hour or two thereafter. Even more striking is the fact that with this single exception—in which case the patient died the next day in coma—all made uncomplicated and complete recoveries within a few days.

This was so good a showing that it must be regarded as in part assignable to good luck. There is certainly no reason to expect that every patient asphyxiated for many hours will recover consciousness thereafter merely because all of the carbon monoxide is removed from the blood; the damage to the brain during the asphyxiation may be too profound to allow recovery. But the fact that none of the patients developed pneumonia, or any of the other common sequelae of asphyxia, demonstrated conclusively that the inhalational treatment has no harmful accessory features.

Indeed, as regards the pneumonia which was formerly a common sequel of gassing, these results suggested that the inhalational treatment might have a distinct prophylactic value; for in one group of forty-three cases (other than those observed in this investigation) in which the victims survived gassing and recovered consciousness without inhalational treatment, the records of Bellevue Hospital showed that fourteen, or 33 per cent, developed a subsequent pneumonia, and ten, or 23 per cent of the total and 70 per cent of the pneumonia patients, died. In striking contrast was the fact that not a single patient treated by the inhalational method developed this common post-asphyxial pulmonary complication.

As a control on these cases it may be mentioned that observations were also obtained on several patients treated with the artificial respiration apparatus, or pulmотор, previously carried by the emergency trucks of the gas company. This apparatus supplied oxygen diluted with air. In one case comparable to the foregoing, the apparatus was applied for forty minutes. An

hour later a blood sample showed that the blood was still 35 per cent saturated with carbon monoxide; and coma continued for twelve hours. Other similar cases were observed. The rate of elimination of carbon monoxide from the blood and of return to consciousness in these cases appeared to be about that which would probably occur if the patients had not been treated at all. Many of the postasphyxial pneumonia cases mentioned above were those that had been treated with the pulmotor.

Besides the 40 cases studied and another 40 recorded as controls in this investigation, we have received during the subsequent years reports on many thousands of others. These reports are made on postal cards, of which a package goes with each inhalator, and on which the principal items of information are indicated. Down to 1936 some 4,000 inhalators have been put into use by the rescue crews of city fire and police departments, city gas and electric companies, hospital ambulances and mine rescue crews. On the average, each inhalator is used on about 100 cases a year. These include some cases so slight that they would recover with merely a headache even without treatment, and other cases in which life is extinct before treatment can be applied, and in addition a wide variety of cases of sudden or acute illness from other causes: electric shock, drowning, pneumonia, heart attacks, asphyxia of the newborn and other emergencies.

Even with all the allowances that the available reports seem to require, it is probable that the number of lives saved from carbon monoxide asphyxia in American cities is now considerably more than 10,000 a year. And this treatment has come into extensive use also in many foreign countries. In 1935 it was officially sanctioned by the Mines Department of the British government.

Chapter VIII

GASES OF PEACE AND WAR

A LARGE part of all the investigations reported in this book were carried on under the United States Bureau of Mines. The work of that Bureau, in the 27 years since it was organized, has been highly effective for greater safety in mining and related industries; and particularly for means and methods of protection against asphyxiation by various gases. In a part of that work, it has been my privilege to participate. The splendid service of the Bureau during the War is a matter of historic interest. And, if saving life from the hazards of industry may rank with service in war, the achievements of the Bureau have formed a no less valuable contribution to the national welfare and to humanity in general in times of peace.

THE UNITED STATES BUREAU OF MINES

In 1910 Congress passed, and the President approved, an Act to establish in the Department of the Interior a Bureau of Mines. The Act provides that there shall be a director of said Bureau, who shall be thoroughly equipped for the duties of said office by technical education and experience, and who shall be appointed by the President, by and with the advice and consent of the Senate. Also that there shall be in the said Bureau such experts and other employees as may from time to time be authorized by Congress. And further that it shall be the province and duty of said Bureau and its director, under the direction of the Secretary of the Interior, to make diligent investigation of the methods of mining, especially in relation to the safety of miners and the appliances best adapted to prevent accidents,

the possible improvement of conditions under which mining operations are carried on, the treatment of ores and other mineral substances, the use of explosives and electricity, the prevention of accidents, and other inquiries and technologic investigations pertinent to said industries, and from time to time make such public reports of the work, investigations, and information obtained as the Secretary of said Department may direct, with the recommendations of such Bureau. And further, besides other duties, that of investigation as to the causes of mine explosions was assigned to this Bureau.

In conformity to the purposes thus defined, the first director of the Bureau, Joseph A. Holmes, requested the American Medical Association to recommend the personnel of a Committee on Resuscitation from mine gases; and in June 1912 he appointed as members of this committee: W. B. Cannon, chairman, G. W. Crile, J. Erlanger, S. J. Meltzer and Y. Henderson. At the request of the National Electric Light Association, this Committee, with the addition of Elihu Thompson, A. E. Kennelly, E. A. Spitzka, W. C. L. Eglin, and W. D. Weaver, served also as a commission to investigate the related subject of resuscitation from electric shock.

After a tour of the anthracite and bituminous coal regions of Pennsylvania to note the conditions in mines, the committee made an investigation of the subject of artificial respiration, which will be considered in a later chapter, and reported that for the restoration of breathing in cases of asphyxiation by mine gases or electric shock, the Schafer prone pressure method of artificial respiration is preferable to any mechanical device. After the report was filed, Director Holmes, on the recommendation of Dr. Cannon, appointed me as consulting physiologist in the Bureau of Mines. Under Director Holmes and, after his

death, under Director Van H. Manning, I had a "roving commission" to investigate any topic on which I believed results tending to save life could be obtained. Both directors gave me their unfailing support during the ten years that I was connected with the Bureau.

ASPHYXIATION AS A HAZARD OF MINING

In large scale accidents in coal mines the usual course of events is that the methane, which exudes from the coal, is ignited by a spark, a lamp, the use of explosives, or in some other manner; and this in turn sets off a wave of ignition of coal dust along the passageways of the mine. Some men may be killed by the explosion of the gas and dust, or by falls of roof; but the majority of the deaths are due to the carbon monoxide which results from the incomplete combustion of the coal dust. In order to rescue these men and fight mine fires, the Bureau early organized rescue crews equipped with what were then called "oxygen helmets," and are now better termed "self-contained oxygen apparatus." But up to the time (1913) of which I write, these apparatus had cost more lives than they had helped to rescue.

Soon after my appointment in the Bureau, in August, 1913, I spent a few days with Haldane at Oxford, and went with him to inspect a coal mine near Doncaster. It was a very deep and gaseous mine, made reasonably safe only by an enormous volume of ventilation and unceasing vigilance. There I saw the conditions and methods of British mining of which everyone has read. I saw the ponies, that live their entire lives at the bottom of the pit, but are healthy and well cared for, and the boys who drive them. I noted the bad lighting that makes nystagmus as common among British miners as it is rare among Americans. And as a particularly interesting experience I saw a "7 per cent

cap" of burning methane above the flame of a Davy lamp: the indication of an explosive concentration of "fire damp."

Another day we went up to London to examine two "oxygen helmets" in which members of the London fire brigade had lost their lives. The authorities had asked Haldane to investigate the cause. By wearing these apparatus ourselves, at Pembrey's laboratory in Guy's Hospital, we soon learned their many dangers and defects. The supply of oxygen was set so low that on any considerable exertion the wearer must collapse. The absorption of carbon dioxide was so imperfect that the wearer could do little but pant. And the helmet leaked so badly that in an atmosphere of carbon monoxide an asphyxiant amount of that gas soon entered.

As often happens when one is doing an investigation for practical ends, an observation of fundamental significance also developed. For this reason I believe, as Haldane did, that it is advantageous to combine fundamental and practical investigation. While wearing one of the apparatus, in which the supply of oxygen had been largely increased, I walked rapidly back and forth in an alleyway beside the laboratory. The world went black before my eyes, but I did not fall. Analysis of the gases in the apparatus showed plenty of oxygen, but a very high concentration of carbon dioxide. The effect was unpleasant, but quite unlike that of lack of oxygen. Then Haldane wore the apparatus and walked rapidly, with his odd swinging gait, back and forth for a few minutes. Seeing him reel, Pembrey and I caught him and removed the helmet. And I saw in the veins of his face and neck, which were bright pink, such venous engorgement as never in any other person, well or ill, before or since. Excess of carbon dioxide had stimulated the venopressor mechanism to maximal activity. And the venopressor mechanism is, beside the heart and vasomotor nervous system, the third major

factor in the circulation: a factor that was then unrecognized or at least undefined.

MINE RESCUE APPARATUS

On returning to America I made repeated visits to the Bureau of Mines Experiment Station at Pittsburgh. There G. A. Burrell, chief chemist of the station, and an enthusiastic disciple of Haldane, collaborated with me; and together we set to work to define the requirements that would make mine rescue apparatus reasonably safe. In this object we were joined from time to time by several mining engineers in the staff of the Bureau, particularly G. H. Deike, J. T. Ryan and J. W. Paul. For all of us carbon monoxide was the enemy to be overcome at whatever cost in work, or risk, or pain. Accordingly we all acted both as observers and as subjects in experiments on asphyxiation and in tests of breathing apparatus under various conditions. It was better, we thought, to be rendered unconscious in experiments in the laboratory than to be overcome far underground in an exploded mine. Deike and Burrell, whose brains—otherwise excellent—were particularly susceptible to anoxemic congestion and edema, still remember their headaches. One of the other men on whom we tested breathing apparatus during vigorous work, a powerfully built workman with extraordinary resistance to high concentrations of carbon dioxide in the breathing apparatus, soon after went insane. I was worried until he showed a triple positive Wassermann.

Our tests of the mine rescue apparatus then in use demonstrated that the wearer could scarcely walk at a moderate pace on level ground in the open air without becoming violently hyperpneic from the accumulated carbon dioxide, or collapsing from lack of oxygen. Even a small crack in the rubber of the mouthpiece, tubes, or breathing bag, easily admitted a fatal

amount of carbon monoxide. Such a defect cost the life of an able young engineer in the Bureau, L. M. Jones, in 1916, just before our work was finished. He was the fourth man that, in the service of the Bureau, gave his life in attempting to save others. He had volunteered to go with a rescue party into an exploded coal mine; and a little crack in the rubber mouthpiece admitted enough carbon monoxide to kill him. In addition to all the other defects of the apparatus then in use, the breathing bag was carried on the chest; and was liable to be deflated while the wearer was crawling through a narrow passage after a fall of roof. If he was in such a position that the bag could not be re-inflated from the oxygen cylinder, and the wearer could not fill his lungs, he would sometimes tear the mouthpiece out of his mouth, even in a deadly atmosphere. To hold the breath with the lungs deflated is beyond human endurance. When used in a wrecked and gaseous mine these apparatus were virtually death traps.

When we had sufficiently defined the requirements that such apparatus should meet, Director Manning appointed W. E. Gibbs, a mechanical engineer, to put these requirements into practical form. The result was an apparatus that automatically adjusted the supply of oxygen and the absorption of carbon dioxide to any volume of breathing and rate of metabolism from rest up to the most intense physical exertion. Some of the engineers had doubts as to how this apparatus would behave under reduced barometric pressure. Accordingly in the summer of 1915 we were ordered out to Colorado for tests on Pike's Peak. There we were met by one of the rescue crews that go to all large mine accidents, and together we carried out tests both at the foot and on the summit of the Peak. These tests showed, among other points, that, if only sufficient oxygen and alkali could be carried,

a man could climb almost to the limit of the world's atmosphere, far above Mount Everest, and not feel the altitude in the least. He would need no acclimatization.

For me that trip to Colorado afforded many profitable talks with men of long experience in the hazards of mines and mine gases, rescue and resuscitation. We all had our meals, and most of us slept, in the railway car of the rescue crew on a siding at the foot of the Peak. But as there were not enough berths for all, Gibbs and I slept on stretchers in the tent that after mine disasters was used as the morgue. However, Gibbs' apparatus passed all tests; and since that time all the oxygen apparatus used by the rescue crews of the Bureau of Mines has been designed on the general lines embodied in the Gibbs apparatus and in its further development by McCaa. The reducing valve invented by Gibbs is also used in the H. H. inhalator.

CHEMICAL WARFARE INVESTIGATIONS

Early in 1917 the full report on "Oxygen Mine Rescue Apparatus and Physiological Effects on Uses," under the names of Henderson and Paul, was published by the Bureau. A few weeks later the United States declared war on Germany; and Director Manning, a very able and energetic executive, made our report the basis of an offer to the War and Navy Departments. He claimed that the Bureau of Mines had on its staff men who were experts in regard to poisonous gases and protection against them; and he proposed that the Bureau should undertake the development of chemical warfare, at least on its investigative side, for the Army and Navy.

As a matter of fact, the Director was "drawing a long bow": the poisonous gases of mines are really very different from those of war, and the oxygen apparatus for rescue work in mines is

entirely different from the gas masks of the battlefield. Yet, as no one in the Army or Navy had then any experience whatever with the new and imperative subject of gas warfare, the offer of the Bureau was gladly accepted by the military authorities. I remember particularly that, when the Ordnance Department asked how we proposed to test poisonous gases in the field, I had hastily to devise some sort of demonstration. It involved the death of a mouse; and, through one of those slips common to scientific demonstrations, the mouse died just before we began to demonstrate. Nevertheless, as the ordnance officer, for whose information we were staging our demonstration, had an antipathy to mice, and indeed to the killing of any animal, he sat so far away that he did not realize what had occurred; and the demonstration was declared entirely satisfactory. However, before the time came for work in the field, we had developed thoroughly practical methods of really doing the job. The young man who assisted me in that demonstration, and who in his excitement killed the mouse prematurely with the strychnine we had substituted for gas, was then only a laboratory assistant. Before the war ended he had risen to be Lieutenant Colonel William S. Bacon, in command of several hundred men at the gas shell proving ground in New Jersey.

Under the general supervision of the Director of the Bureau of Mines the War Gas Investigations were carried on for a year before the Army took over the entire staff as the Chemical Warfare Service; and all my scientific colleagues became—nominally—soldiers. During that year of development Burrell was in charge of chemical developments and chief of the entire research division. Under him my associates and I had charge of a side of the work that we, at least, considered quite as important as that of the chemists; for without the aid of a toxicologist, a

chemist cannot tell whether his products are poisonous or not. For our principal laboratory we had the buildings of the American University just outside Washington; and there were a number of other stations at other universities where special groups were organized, that had to be inspected frequently. In addition there was the aviation laboratory, referred to in chapter IV at Mineola, Long Island, N. Y., which was at first also financed under the Bureau of Mines. Within the year we built up an organization of several hundred scientific men, most of them young. All of those in my division were appointed because I knew them and without the delays involved in civil service examinations. They all made good.

One of our jobs was to test on animals, and sometimes on ourselves, all the poisons that the chemical division developed. For each substance we determined three standards: (1) the amount that would kill or incapacitate even after a short exposure—the standard for the battlefield; (2) the amount that could be tolerated for a short period, without serious injury—the standard for us experimenters in the laboratory; and (3) the amount that could be tolerated for long exposures—the standard for the workmen in the factories producing these poisons in quantity. Three such standards are essential in the use and control of all poisonous substances, whether in war or in industry. A great part of all modern industry is chemical; and the majority of all chemicals are more or less poisonous. Their hazards can be controlled only on the basis of such standards; and for many industrial chemicals the requisite standards have been developed since the War. Such standards apply even to alcohol as a beverage, and are the only sound basis for the control of its abuse.

Fortunately during the war investigations we had no fatal slips. The only serious one was early in the work, when an

accidental dose of one of the so-called "gases"—really volatile liquids—caused Haggard to lose 40 pounds in a week or two.

Another of our jobs was the development of a therapy for various kinds of gas poisoning. Most of the war gases are of the class of irritants and induce pulmonary edema. The victim drowns in the fluid exuding from the blood in his burnt lungs. Accordingly F. P. Underhill worked out a treatment—bleeding and saline infusion—which he believed would diminish the mortality from pulmonary injuries induced by the war gases. And Haggard showed that the point in the respiratory tract—larynx, trachea, bronchi, or lungs—upon which any one of these substances acts, is determined by its solubility; the least soluble acting most deeply. (See our book, "Noxious Gases.")

For the treatment of gassed soldiers overseas and poisoned factory workers at home, I designed an inhalator for the administration of oxygen: the apparatus that after the War was developed into the H. H. inhalator.

DEVELOPMENT OF THE AMERICAN GAS MASK

The first task was the development of an efficient gas mask; and here the experience at the Pittsburgh Experiment Station was useful. The British gas mask had a fairly good absorptive power; but Haldane had not been consulted, and the canister, through which the air was inhaled and in which the gases were absorbed, imposed so high a resistance to breathing that the wearer could make little physical exertion. He certainly could not "go over the top" in a charge. Starting from mere reproduction of that mask, American ingenuity and thoroughness have developed since the War a splendidly efficient mask that quite properly bears Burrell's name, and is today of immense value in protection against industrial gas hazards. But of that future

success we then of course knew nothing; our first masks were very defective.

The defectiveness of the first lot of 10,000 masks manufactured in this country is a topic of peculiar interest to me, as it fell to my lot to wear one of the first two of those first 10,000. The reason for this was that, in addition to the routine chemical tests, it was decided that out of every large shipment for the use of the soldiers in the trenches a certain number of masks, selected at random, should be worn in a gas chamber here in America before the others were sent overseas. Some twenty young chemists under Fieldner were told off for this duty; and as they looked forward to it with evident anxiety it was decided that one of the higher officers in the organization should give them a lead. It was quite obviously my job.

I cannot say that I anticipated the ordeal with pleasure; but it had to be done. Accordingly, with my coat off and the mask on, I went into a big steel cylinder in the old Arsenal grounds at Pittsburgh, shut the door, sat down on a soap box and emptied two carboys of chlorine gas into the air of the chamber. As the green gas eddied about me, it felt warm and smarting on my skin. It even liquified the tin on the outside of the canister. There I sat, or stood, for 15 minutes, while those who were later to be regularly engaged in such tests—generally less severe—were looking in at me through the windows. I remember wondering what was the quite familiar emotion that had me in its grip: wondering until I recognized it as the feeling I always have before an after-dinner speech. I was very much scared.

Luckily I suffered nothing worse than to have my clothing decolorized and partially rotted. In this I was fortunate, for the other mask of those first two was afterwards found, under chemical test, to be so defective that, had I chosen it, I should

probably not now be writing this book. And acute bronchopneumonia is not a pleasant mode of death.

POISONED BULLETS

Before America entered the War my sympathies had been mainly with the Germans: not that I thought it was at all our duty to aid them against the Allies, or that I wished them to win; but that I had lived and studied in Germany and admired their science and orderliness, and their personal kindness. I thought that they must inevitably lose the War; and as one born and raised in a southern state, I never doubted that the brutality visited on our South by our North after our Civil War would be repeated in one form or another by the English and French on Germany: as it was. Yet I believed that once we Americans were committed to the monstrous absurdity of mixing ourselves in the European dog fight, each individual American should discard all doubt or hesitation and work or fight as hard as ever he could. And that meant doing the utmost to kill Germans.

To that end I worked to the limit of my strength and, indeed, far beyond. One incident, not previously published, is typical of what we all did; for we chemists and toxicologists had none of the silly qualms of those who think that it is legal warfare, right and proper, to blow off a man's face or eviscerate him with high explosive; but that it is brutal to poison him. Accordingly I took it as quite in the day's work when there came down to me from the War Department, through the ultra-confidential channels used for important military secrets, an order to arrange for the development of some poison to be applied to bullets, so that every wound, even the smallest scratch, would be fatal. Deaths would thereby be increased five or ten fold; few or none of the wounded would recover, and the enemy's army would be correspondingly diminished. I was to find and appoint the man

whose special knowledge best fitted him to develop that substance. I knew exactly the man. I called him by telegraph and saw him. And he did the job; yet of all the scientific men I know he is—in peacetime—one of the gentlest and most humane.

As matters turned out, the War ended before any of the combatant nations had resorted to the supreme atrocity of poisoned bullets.

HELIUM FOR BALLOONS

Helium had then recently been found in the petroleum of a Texas field. As I remember it, Burrell was the first to suggest that balloons inflated with this gas would be free from the risk of fire involved in the use of hydrogen. To this suggestion two of our most eminent physicists offered the objection that as the weights of hydrogen and helium are as 2:4, helium would have only half the lifting power of hydrogen. Burrell met this objection by showing that, as the relative weight of air is 28, the lifting power of hydrogen is $28 - 2 = 26$, and that of helium $28 - 4 = 24$. Helium has therefore nearly as great (i.e. 24:26) a lifting power as hydrogen.

The next event was the arrival in Washington of two English naval officers. With one of the higher officials of our government presiding, we had an ultra-secret conference on the subject of "X gas" as we called helium, in order to fool any German spy that might be hidden under the desk. All day our presiding official, who was a first-class diplomatist and executive, guided the conference. Then we adjourned and after every one else had left, he drew me aside, and said in my ear: "That X gas: is that the letter X?" And I assured him that it was. Certainly no spy under the table would have had much information to transmit to Berlin on that subject.

Now, after the recent disaster in which the Hindenburg was

destroyed by fire in New Jersey, our government has, I am glad to say, decided to allow helium to be supplied for future zeppelins. And it is not called "X gas."

PEACETIME ACHIEVEMENTS OF THE BUREAU

It would require a chapter to itself—indeed an entire book—to tell of all the contributions that the Bureau of Mines has made in the peacetime war in which carbon monoxide is the enemy. When the Commission on Resuscitation from Mine Gases went through the mining region back in 1912, the miners were all using open-flame lamps fastened on their caps; and the flame occasionally started a fire or an explosion. Now those oil lamps are replaced by electric bulbs and storage batteries. In 1912 the simple old-fashioned safety lamp in which the flame was surrounded by a wire gauze, as invented by Sir Humphrey Davy a century before, was still used, not indeed for light, but to test the inflammability of any pocket in the roof of a coal mine where there might be methane. Now Burrell's analyzer has replaced the Davy lamp. Now also each American coal miner carries in his pocket a little apparatus, the "self-rescuer," that he can slip on and be protected long enough to escape, after a fire or explosion, even through an atmosphere high in carbon monoxide. Most important is the introduction, largely through the work of Mr. G. S. Rice, Chief Mining Engineer in the Bureau, of the practice of stone dusting in the passageways of our coal mines. By this means the coal dust is diluted and its explosion and combustion to carbon monoxide is prevented.

MINE SAFETY APPLIANCES COMPANY

All of these and other advances in the conflict against carbon monoxide would, however, be mere matters of publication, not of

practical achievement, if it were not for the development of the Mine Safety Appliances Company. This offshoot of the Bureau of Mines was organized by two of the engineers formerly in the Bureau, G. H. Deike and J. T. Ryan. Although they had withdrawn from official government service, their establishment of this company to manufacture and supply the apparatus that the investigations of the Bureau demonstrated to be needed by the mining industry, should count as a major scientific and public service. It is mainly due to them that American apparatus in this field has attained a high degree of perfection.

It is customary for so-called "pure scientists" to receive the public credit for the advances they devise. But such advances would never become effective, if it were not for the support given by such commercial organizations as the Mine Safety Appliances Company in America, the Siebe Gorman Company in England, and the Draeger-Werk A. G. in Germany. It is such organizations as these that make the results of scientific investigations available for practical application. In particular it was the work of H. J. Segrave, as agent of the Mine Safety Appliances Company, that, more than that of anyone else, has introduced the H. H. inhalator into general use. Without this contribution the inhalational treatment of carbon monoxide asphyxiation would now be merely embalmed in the pages of medical journals.

RESUSCITATION OF THE NEWBORN

When the Bureau of Mines and the Mine Safety Appliances Company were organized nothing was further from their purposes than to make a major contribution to obstetrics. Yet such a contribution has come about. Early in January 1926, Haldane and I were in Paris on our way to Egypt. At a news stand I bought a copy of the Chicago Tribune, Paris edition. In

the center of the front page, in a small block of space, it was announced that the "Chicago Fire Department rescue crews save many newborn babies that otherwise fail to breathe." In this way the inhalation of carbon dioxide and oxygen was first introduced into its most important field of usefulness.

Chapter IX

HOW BREATHING BEGINS AT BIRTH

ONE of the oldest problems of science is: Why does the baby begin to breathe at birth? The purpose is clear; but the cause and means are obscure.

Half an answer has long been available. It is well established that for many weeks or even months before birth the fetus makes distinct rhythmic respiratory movements. Ahlfeld in 1905 published excellent graphic records of these movements. They were taken from the surface of the mother's abdomen. And a number of recent investigators have obtained moving pictures of respiratory movements in animal fetuses delivered by Cesarean section in a bath of warm saline. But these movements are ineffective in expanding the lungs and keeping them expanded. The question then becomes: How are the feeble and ineffective respiratory movements of the fetus transformed into the effective breathing of the newborn?

The answer, I believe, is to be found in the fact that a certain function is deficient in the fetus; and that this function is quickly developed at birth and is then continually maintained throughout life. It is a function of critical importance alike for respiration, circulation and metabolism: the function of muscle tonus.

RESPIRATORY MOVEMENTS BEFORE BIRTH

Early in its development, the fetus begins to make occasional movements. The mother feels life within her.

The earliest of these movements occur almost as soon as the outgrowing nerve fibers make contact with the embryonic muscles. Later, but still early in fetal life, the various reflex mech-

anisms are organized. Observations have been made also by Hooker and others upon human fetuses that, for surgical reasons, have been removed before the seventh month. Although their reactions are generally distinctly depressed by the drugs administered to the mother, reflex movements are generally easily elicited. A light touch upon the palms of the hands or the soles of the feet may induce typical grasping movements even in a fetus of ten or eleven weeks; and a length of only 6.5 centimeters, or 2.8 inches. Sucking movements of the lips may occur in one that is even younger.

Movements of the thorax and abdomen of the pattern that, if the child lived, would later be used in breathing, are slower in appearing; but they are nevertheless generally distinct by the fifth or sixth month. In the last months of pregnancy the contractions of the diaphragm of the fetus are distinctly rhythmic. Some of Ahlfeld's curves even show Cheyne-Stokes respiration; others present hiccups (*singultus*) in the fetus as distinct as one sees in a baby.

These fetal respiratory movements are, however, too weak to dilate the lungs with the amniotic fluid. That fluid is far more viscid than air; and until the fetus has attained full development it has little strength. Even the baby at full term has to exert the whole force of the respiratory muscles to inhale air; and many inspirations are required before the lungs are fully dilated. It is now known that for some weeks before birth a small amount of the fluid is inhaled. It is however immediately absorbed into the blood—for the lungs are the most absorptive organs of the body—and excreted through the kidneys, as is the amniotic fluid that is swallowed. It is only when the circulation is obstructed that strong inspirations—*asphyxial gasps*—are induced. Even then it is the obstruction to the circulation and consequent

cessation of the supply of oxygenated blood to the brain that kills. The fetus cannot drown in the amniotic fluid.

Interesting observations have recently been reported by Snyder and Rosenfeld upon rabbits, in which animals the respiratory movements of the fetus may be observed through the thin wall of the uterus after the abdomen has been opened in a bath of warm saline, or even through the wall of the unopened abdomen. Narcotics and anesthetics administered to the mother in amounts that induce only light anesthesia, and do not at all impair her respiration, are nevertheless found to depress seriously, or even to inhibit completely, the intrauterine respiration of the fetus. Administration of a gas mixture containing only 4 per cent of oxygen to the mother induces a marked increase of her breathing, but only a slowing or cessation of the fetal respiratory movements. Hyperventilation of the mother's lungs results in a distinct slowing of the respiratory movements of the fetus or complete apneic standstill. Administration of carbon dioxide up to 7.5 per cent to the mother may, or may not, induce an increase of the rate of the fetal movements, but not active breathing. Clamping the umbilical cord, on the contrary, always initiates strong respiratory efforts—gasps—in the fetus, provided that the mother is not too deeply anesthetized. Their observations lead Snyder and Rosenfeld to agree with those who regard the onset of postnatal respiratory activity, not as an event initiated abruptly at birth, but rather as a transition from the weak respiratory movements discernible during intrauterine life.

Although the fetus moves, its muscular activity is not considerable. Floating, as it does, in a warm fluid, its heat production and metabolism are low; and its oxygen consumption and carbon dioxide production are correspondingly small. For its small gaseous exchange the placenta provides so effectively that

the pressures of both oxygen and carbon dioxide are nearly the same in the fetal and maternal blood in the umbilical and uterine veins. Analyses by Barcroft and others indicate that the fetal blood has a higher affinity for oxygen than the maternal blood, and that the blood in the umbilical veins has a correspondingly higher content of oxygen than that in the uterine veins: an obvious advantage to the fetus. But as the pressure of oxygen in the fetal blood cannot be higher than that in the uterine veins, the fetus is supported on blood that, at least in respect to the pressure of oxygen, is venous blood.

The pressure of carbon dioxide in the fetal blood is likewise essentially that in the venous blood of the mother. On such a supply of carbon dioxide the mother breathes actively; and after birth the infant will also. The failure of the fetus to breathe actively in utero cannot then be due to a lack of this chemical stimulus. Cohnstein and Zuntz found evidence that the sensitivity of the respiratory center before birth is low, and that even after birth it rises only gradually to normal. Yet this condition scarcely affords a sufficient reason for the low activity of the respiratory muscles of the fetus. The reason lies, rather, I believe, in the fact, which I have demonstrated for adults, that without tonus real breathing is impossible. And Barcroft and Barron have found that the fetus lacks tonus.

Barcroft's observations have been made chiefly upon sheep at various stages of gestation. The fetal lambs are delivered by Cesarean section, and the placental circulation is maintained while the mother's body is immersed in a bath of warm saline. These observations were made by Dr. D. H. Barron in Professor Barcroft's laboratory by Adrian's method of recording the electrical state of muscles. Barcroft interprets the observation as showing how the organism, that up to birth has been kept warm

in the mother's body, at birth begins to develop its own heat; for tonus involves the consumption of oxygen and the liberation of heat. He says "So long as the fetus is in its normal environment, or in a bath of warm saline with the placental circulation unrestricted, the fetal muscles are entirely devoid of tone. Take the fetus out of the saline and expose its skin to the air; tone at once appears in its muscles, only again to be abolished by replacing the embryo in the saline."

THE SIGNIFICANCE OF TONUS

When I first read these words a few months ago, I had only recently, but as the result of many years of varied observations, reached the conception that in the adult tonus is absolutely essential, not only for breathing, but also for the maintenance of the circulation. When tonus fails these functions are stopped. It now becomes evident that this conception affords also the explanation why the fetus in utero cannot breathe, and why the newborn baby can. The baby has tonus; the fetus has not.

Some of the grounds for this conception, as it applies to adults, are given in various connections in other chapters. In order that a man or baby may be able to ventilate the lungs by breathing, the respiratory muscles, particularly the diaphragm, must be maintained in a sufficient degree of continuous contraction or tonus to keep the lungs expanded. The maintenance of a large volume of "stationary" air in the lungs is essential for normal respiration. In proportion as a man who is injured or ill loses tonus, his lungs are deflated. Without tonus, the lungs of the newborn would remain in the fetal state of atelectasis or would revert to that state. Furthermore, without tonus or with insufficient tonus, the muscles throughout the body cannot develop an intratissue pressure sufficient to maintain the venous

return of blood to the heart; and the circulation fails. This condition in an adult is one of shock, as will be set forth in a later chapter. The corresponding condition in the newborn is that of asphyxia pallida.

In Barcroft's description of the development of tonus in a fetal lamb when it is lifted from a warm saline bath into the air, the influence of cutaneous stimulation is shown. The degree of tonus is slight; for it is abolished by replacing the fetus in the bath. Yet the fact that any such effect at all is induced, reminds one of the ancient practice, not yet extinct, of dipping an apneic baby into cold water. From observations of M. O. deAlmeida we know that a frog has a higher degree of tonus when lying on a hard surface than when floating in the water. In healthy men, as Oughterson, Searle, Greenberg, and I have recently shown, the mere stirring of the air in a warm room by means of an electric fan is sufficient to induce a small, but distinct, increase of tonus, as indicated by the intramuscular pressure in the biceps.

We need not therefore conclude from the interesting observations of Barcroft and Barron that chilling the skin is more than one of the elements in the development of tonus. At birth a number of other reflex and chemical stimuli come into play. The most effective of these stimuli are induced by the fundamental readjustment of the circulation. The blood stream, that in the fetus was short circuited from the right heart to the left and from the pulmonary artery to the aorta, is now first in full volume driven through the lungs. Through the umbilical veins the placenta drains its blood into the baby: a self transfusion that on physiological grounds should be allowed to go virtually to completion before the cord is severed. Arterial pressure rises to a new level, much higher than before. And, as usual in physiological adjustments, each of these conditions reacts upon all the others.

Confining our attention now to respiration we may illustrate the relation of tonus to breathing by a comparison. The atonic fetus and its ineffective respiratory movements are like an automobile standing still, but with its motor running gently, or as we say, "idling." As soon as the lungs are inflated and kept inflated by tonus, active breathing replaces mere "idling." Thereafter, until tonus is abolished by death—it may be in extreme old age—the diaphragm is never again completely relaxed.

TWO WAYS OF BEGINNING TO BREATHE

The first cry of the newborn is a dramatic event. It is so dramatic that we overlook the fact that, as a cry requires an expiration of some volume, the child must previously have expanded its lungs by at least an equal volume. It is the preceding inspiration or inspirations that are really important. They are made quietly—so quietly that they pass unnoticed. They are continuations and progressive augmentations of the fetal movements supported now by increasing tonus. The first cry, no more than any later cry, means anything other than that the child is uncomfortable or angry or both. It has in effect been roughly awakened from a very sound sleep. The cry shows that the child is breathing; but it is an accessory, not an essential, in the development of breathing.

Very different is the beginning of respiration in an asphyxial baby that is resuscitated by the old rough methods of stimulation, or that manages to recover by itself. In such cases respiration begins with gasps: first a gasp followed by a pause, then another gasp, and a somewhat shorter pause, then perhaps two gasps together, and so on, until a more normal form of respiration is established. Such gasps occur in the late stages of all forms of asphyxia. The "death rattle" of a dying man is a gasp; and

"air hunger" under a fatal hemorrhage terminates in gasps. Even the ambulant cardiac patient, whose impaired circulation renders him slightly anoxemic, exhibits occasional gasps, as do also those otherwise normal men who are so sensitive to their supply of oxygen that they sigh at intervals. In all cases the gasp consists in a quick deep inspiration followed immediately by a passive expiration. It is not induced by carbon dioxide; for gasps may occur during an intense experimental acapnia. They are anoxial; but yet reflex. When a patient stops breathing on the operating table, it is often possible to induce a gasp by pulling the tongue or dilating the anus, or by some other form of intense, even painful, sensory stimulation.

Barcroft describes the first breath of an asphyxial lamb born of a narcotized mother as follows: "It is a gasp involving a great proportion of the muscles of the body. It may be questioned, indeed, whether the fact of air being introduced into the chest is much more than incidental. I mean that a general wave of contraction passes over a great part of the musculature of the body and since the diaphragm and intracostal muscles are powerful muscles the chest is opened. This gasp, in fact, seems to resemble in every possible way the dying gasp of an animal subjected to oxygen want, say by cyanide poisoning or even deprivation of oxygen in the air; this is true in some detail, even to the order in which the muscles contract. From the point of view of the fetus, the gasp is an index pointing, not to life, but to death, and we are faced with the remarkable paradox that the dying gasp of the fetus is the earnest of life to the individual."

For a time Barcroft believed such asphyxial gasping to be the normal initiation of breathing. The mothers (ewes) were narcotized and the lambs exhibited typical narcotic asphyxia. When in later experiments, however, spinal anesthesia was sub-

stituted for general narcosis, the Cesarean lambs developed respiration quite normally and without either apnea or gasps. Similarly in babies it is not those that are cyanotic, but those that are bright pink that begin breathing and cry almost as soon as their heads are in the air. On the other hand, too many American babies now begin life in a state of narcotic asphyxia similar to that of the asphyxial and gasping lambs.

As regards the causation of these gasps, Barcroft finds that, when chemicals that induce a formation of methemoglobin are injected into the umbilical veins, typical gasps occur. Wilson has shown in infants that an intravenous injection of the drug lobelin induces vigorous gasps; and lobelin acts, as Cordier and Heymans report, through stimulation of afferent nerve endings in the sinus caroticus. In addition the manipulations long used in the resuscitation of the asphyxial newborn may teach us that any strong sensory stimulation—slapping, plunging in cold water, kneading, etc. may also excite reflex gasps.

Between the normal, or tonic, beginning of breathing and that by gasps there are many intermediate gradations.

THE RESPIRATORY MOTOR

With these facts before us we may aptly compare the beginning of effective breathing to the starting of an automobile. When the car is standing still, but with its engine running gently, we speak of its motor as "idling." And so it is with respiration before birth. Then suddenly at birth strong sensory stimuli act upon the skin. Muscular tonus is induced, expansion of the lungs begins. And the child breathes.

The analogy may be carried even further. The baby that is born in asphyxia, resembles a motor that is stalled. And as with the stalled motor, so with the asphyxial baby, a restoration

of activity may be induced in two ways. The motor may be cranked and spun until, in spite of poor carburetion and ignition, a "cough" is induced. The baby likewise may be manhandled, as it formerly commonly was, until a reflex gasp is elicited.

Better methods are, however, now available both for the motor and for the baby. In the car the carburetion and ignition may be adjusted so perfectly that the motor starts at a touch. In the baby the oxygen and carbon dioxide that its nervous system need may be supplied by inhalation or insufflation, as has now become the accepted practice. Resuscitation is thus effected without "cranking."

GRADUAL INFLATION OF THE LUNGS

It was long assumed that the initial gasp overcomes atelectasis and inflates all parts of the lungs at once. Such is by no means the case. The inflation develops gradually in essentially the same manner as that seen when the thorax of an animal has been opened, complete deflation induced, and the lungs then reinflated by a succession of puffs of air blown into the trachea by a bellows. At the first puff small areas around the larger air tubes swell and become translucent; but the rest of the lungs, even parts next to the now dilated areas, remain opaque and nearly solid. The walls of the smaller tubes and vessels are glued together by their viscid, sticky secretion. At the next puff the dilated areas spread and some additional areas open; and at each succeeding puff yet other areas are dilated, until only scattered patches of atelectasis remain. Then these also clear.

Thus the dilation proceeds, not as a uniform and continuous process, but by many small steps. Faber and Wilson have found that even under a pressure of 35 cms. of water column the moist surfaces of the finer tubes and air spaces are only gradually

separated, although an intrapleural negative pressure of only 13 to 16 cms. is required to keep them distended thereafter. When the lungs are inflated with a bellows, and the adherent walls of the air tubes and chambers are separated by a positive pressure of air in the trachea, Wilson reports that they are easily torn. In the newborn they are normally separated only by the negative pressure induced in the thorax by the pull of the diaphragm, and by the pressure of the atmosphere down the trachea and bronchi. The atelectatic lungs of the fetus are more fleshy and less membranous than those of an adult animal or man, and correspondingly more difficult to dilate. The respiratory muscles are new to their function, and often in weak infants have scarcely sufficient impulse to perform it.

On the first day of life the volume of the breath is extremely small. Twenty minutes after birth the breath has been found to be only 17 cc.; three hours later, 21 cc. and six hours after birth 36 cc. A week later, as the average for many normal babies, Dohrn found the tidal air during quiet breathing to be only 40 cc. And he adds measurements which show the highly significant fact that crying increases the volume only about a tenth on the first day and a fifth on the seventh. Evidently the ancient practice of making the baby cry to dilate its lungs is not very efficient.

Observations by means of the X-ray have shown that there are wide variations in the length of time required for full dilation of the lungs. "In some cases of normal easy delivery with the child in good condition"—as Wasson reports—"the lungs gave the appearance of full expansion within five minutes after delivery. Again in similar cases of easy delivery, but especially in those of prolonged difficult delivery, the expansion of the lungs was found to take place slowly, leaving entire lobes atelectatic

or with only scattered areas of atelectasis We called the lung fully expanded when there was air throughout all the parenchyma and no evidence of scattered density suggesting remaining atelectasis. The interval of time for this to take place ranged from five minutes to two weeks." More recently Dunham has published excellent roentgenograms showing all stages from opacity through haziness to clearness in the infant's lungs; and these appearances correlate closely with the position of the diaphragm and the angle between the ribs and spine—as indications of chest expansion.

The evidence from autopsies reported by Cruikshank and others fully confirms the view that, even in babies that at birth are judged wholly normal, complete dilation of the lungs may not be attained for hours or even days. In the weak and particularly in the premature the occurrence of cyanosis is the common indication of the continuance of atelectasis.

MUSCLE TONUS AND THE CIRCULATION

At birth the circulation undergoes changes that are quite as fundamental as those of respiration. And one of these changes is dependent upon the development of muscle tonus.

As the placental vessels contract, the blood is sent in full volume through the lungs. Previously the flow of blood back and forth between the fetus and the placenta has needed no support by muscle tonus. But at birth the circulation takes on a new vigor. The left side of the heart comes into action and arterial pressure rises to a higher level. For this adjustment a full venous return is essential; and such support for the circulation can be induced and maintained only by muscle tonus and an intra-tissue pressure throughout the body. And this requirement is shown by the fact that whenever, because of asphyxia

during birth, tonus fails to develop the flaccid baby exhibits the infantile form of shock, asphyxia pallida.

Before birth the fetus, floating in a fluid at body temperature, need produce little heat of its own. After birth the baby must assume the maintenance of its own heat supply to compensate for a continual loss of heat to a generally colder world. Normally the requirements of body temperature are soon met by the establishment of a basal metabolism sufficient to meet this requirement. And in the control of metabolism muscle tonus plays a major part. The tonic pull of the muscles involves a consumption of oxygen, production of carbon dioxide, and liberation of heat. And all these related functions are thus influenced by the nervous impulses from the motor centers in the spinal cord that chiefly induce tonus.

In respect then to the three vitally important functions of respiration, circulation and metabolism, the fetus has little need for tonus. But, if the baby is to establish and maintain its independent life, tonus is essential. In fact the difference between the vigorous child and one that barely lives even in an incubator—the case of “Lebenschwäche” as the Germans term it—probably consists chiefly in the degree of their tonus. In the premature baby with a subnormal tonus the lungs may remain partially unexpanded for weeks. Along with the continuance of atelectasis the circulation is weak. Metabolism and the oxygen consumption are low; and the heat production is slight. Correspondingly the production of carbon dioxide is inadequate to produce full breathing; cyanosis develops; respiration is further depressed, and asphyxia ensues.

Chapter X

ASPHYXIA OF THE NEWBORN

BIRTH is by far the most dangerous event in life. It involves three successive periods, each of which now has a mortality that greatly exceeds that of any subsequent month. Each of these periods has its special and distinct hazards, and each requires its special means of prevention or counteraction. Yet all of these hazards are alike in one respect: they all lead to asphyxia.

The first of these three periods begins with the onset of labor in the mother and ends with the delivery of the baby. During this time the mother must be considered ahead of the child. Yet in respect both to drugs and manipulative interference the child deserves much more consideration than it now conventionally receives. It is a perverted humanity which provides for the mother an abbreviated, painless, or even entirely amnesic labor at serious risk of her gaining only a dead baby.

The second period is brief: little more than a quarter of an hour, or at most a half hour, after birth. Within that time respiration must be established, or life is extinguished. The problem of inducing breathing in an apneic baby is in the main like that of resuscitating a victim of any other form of asphyxia or narcosis. Formerly rough handling was employed in the attempt to excite reflexes. Now such practices have been replaced by measures of assistance based on the chemical regulation of respiration.

The third period follows the establishment of respiration and may continue for several days, or for two or three weeks or even a month. It ends only when the development of vitality—as

expressed in tonus, respiratory metabolism and heat production —has overcome the last trace of atelectasis, completed the inflation of the lungs and eliminated the risk of pneumonia. Until recently, even in the best obstetrical services, the hazard of a continuance of atelectasis was generally ignored. In many large maternity hospitals it was almost a matter of course that most of the premature babies that escaped the hazards of the first two periods must die in this neonatal period. It is the mortality of this period that can be most effectively decreased.

NATAL AND NEONATAL MORTALITY

For 1927 the Bureau of the Census reported for the birth registration area, or 87.3 per cent of the population, 2,137,836 live births and 82,931 stillbirths: nearly 4 dead to each 100 alive. Of the live births 1.4 per cent died during the first day; 1.2 per cent in the next 6 days; 0.4 per cent in the second week: a total of 3 per cent in the neonatal period. In contrast only 3.4 per cent died during the remaining 50 weeks of the first year of life. Together the stillbirths and those of the neonatal period amounted to 7 per 100 births, or two-thirds of the entire mortality of the first year. If the statistics for stillbirths were more accurate, these figures would probably be still higher; a tremendous mortality.

It is probable also that a considerable number of those listed as stillbirths and of those that died in the first day were merely cases of asphyxia that might have been resuscitated if efficiently treated. Premature birth is given as the largest single cause of death, 35,916. But prematurity cannot be accepted as in itself a cause; for unless a premature child fails in some function—generally that of respiration and the underlying functions of tonus and the gaseous metabolism—it lives.

In Chicago where the Board of Health is making a special effort to lower the natal mortality, there were, during 1935, 2.69 stillbirths to each 100 live births. And of the latter 2.75 per cent died in the first month and only 1.26 during the next eleven months. There were 795 premature births of which more than a tenth died within an hour and nearly 70 per cent within 24 hours. Unrelieved atelectasis, often unrecognized until autopsy, was demonstrated in a large proportion of these babies. Improper methods of resuscitation were used on 149 babies, and among the premature there were 41 instances of excessive drugging of the mother as a contributing factor in the infant mortality. Perhaps the most significant figures in the Chicago report are the mortalities for the first month of life 3.7 per cent for the year 1925, and 2.75 per cent for 1936 in comparison to those for the remaining eleven months of the first year, 3.77 per cent for 1925 and 1.26 for 1935: a moderate decrease in the first month in comparison to a huge decrease for the next eleven months.

A mortality of 4 per cent, or even of 8 per cent sounds low in comparison to that of some of the virulent diseases. But the mortality of such a disease as typhoid or pneumonia affects only those who become infected. Birth, on the contrary, is not a disease. All must be born.

There was a time, not many decades past, when the newborn were subject to another hazard that has now been generally eliminated. At that time many cases of blindness resulted from infection of the eyes at birth. If measures to insure expansion of the lungs were as much a part of the routine treatment of the newborn, as is now the disinfection of the eyes, lives would be saved as effectively as blindness is now prevented.

The high mortality of the neonatal period is notable when

compared with the great decrease of infant mortality in the rest of the first year of life. That decrease has been effected by measures to prevent gastro-intestinal disorders. In the summer of 1910 in the city of New York, such disorders killed 3,598 infants; in the summer of 1935, this toll was only 166. As the measures that have accomplished this decrease of the post-neonatal period—chiefly the pasteurization of milk—have not affected the mortality of the neonatal period to any comparable degree, the inference is clear: neonatal mortality is mainly respiratory.

THE CAUSES OF ASPHYXIA

Up to the time when the circulation through the umbilical vessels ceases, any alteration in the gases in the maternal blood immediately affects the gases in the blood flowing from the placenta to the fetus. If the mother, because of prolonged labor due to narcotics, exhaustion, loss of courage or lowered muscle tonus, becomes cyanotic or pallid, asphyxia tends to develop in the fetus. If the fetus becomes dangerously anoxic, its heart rate is slowed, its capacity to develop tonus at birth is lowered and the sensitivity of its respiratory center is depressed.

Similarly if any considerable degree of acapnia is induced in the mother by overbreathing because of pain, fear, or the excitement stage of anesthesia, this condition tends to induce apnea in the baby. Acapnia tends to induce anoxia in several different ways beside depression of respiration. Without a full supply of carbon dioxide in the blood there cannot be a full supply of oxygen to the tissues. Acapnic blood in the mother yields its oxygen less readily to the fetal blood in the placenta. Acapnia depresses the maternal circulation, including that to the uterus. It lowers the tonus of the respiratory and abdominal muscles;

and the tonus of those muscles plays an important part in the expulsive efforts of parturition. Acapnia probably decreases the tonic contractions of the uterus in the same manner that I found it (in 1909) to decrease the tonus and peristalsis of the gut. The administration of oxygen toward the end of a prolonged and difficult labor has been recommended. But even more important is the use of carbon dioxide, either by rebreathing along with nitrous oxide analgesia, or by brief periods of inhalation of 5 per cent of carbon dioxide in air or oxygen, as recommended by McCormack. By increasing the tonus of the muscles, it augments the circulation. By increasing respiration it provides for a full supply of oxygen in the blood both to the laboring muscles of the mother and to the placenta and fetus. The child is thereby rendered more fit and inclined to begin breathing as soon as it is delivered. The risk of premature respiration from over-stimulation of the respiratory center of the fetus is nil.

The contractions of the uterus force its contents out of its cavity essentially as Bayliss and Starling showed that the contractions of the gut squeeze its contents onward. The peristalsis of the intestine consists in a slowly advancing area of contraction preceded by an area of relaxation. Similarly, although more slowly, each "pain" during the first stage of labor involves the contraction of the body of the uterus containing the fetus and placenta, and a gradually increasing relaxation and dilation of the cervix through which the baby must pass. For reasons both of anatomy and mechanics it appears improbable that either the uterus or the gut can add appreciably to the force that—in defecation and in the second stage of labor—finally expells their contents from the body. That force is almost wholly the pressure produced by contraction of the abdominal and thoracic muscles, but not the diaphragm. The pressure thus induced is

essentially the same in parturition, defecation, and Valsalva's experiment. It can, in fact, be measured as the maximum force that can be exerted by blowing into a manometer. It is of the order of 80 to 120 mm. of mercury. The force that sends the child into the world is then the difference of pressure between that which is thus produced in the abdomen, plus that of the atmosphere, and that of the atmosphere alone on the perineum.

Normally each period of breath holding and expulsive effort is followed by a short period of compensatory hyperpnea. If, because of excessive suffering or fatigue, the breath holding is insufficient and the hyperpnea excessive, acapnia is induced and progress ceases. It should be possible to devise an arrangement to use positive air pressure above the hips, or negative pressure below, to aid delivery, instead of forceps, when the woman becomes fatigued, and aid is needed: a device like the Drinker respirator.

So long as the fetus floats free in the amniotic fluid, no change of pressure can seriously affect its circulation. In the second stage of labor, however, during the passage of the child through the unyielding and sometimes narrow pelvis, it may be dangerously compressed. The flow of blood through the umbilical vessels may be obstructed, or the head may be deformed. The blood supply to the vital centers in the medulla may thereby be more or less completely shut off; or an intracranial hemorrhage may be induced. A prolonged delivery is harmful to both mother and child. Its termination by the use of forceps has therefore a value for both. The same considerations support the contention of Thoms that the usual methods of external pelvimetry should be replaced, at least in all primipara, by the roentgenometric method of measurement. If a serious disproportion is found, abdominal delivery may then be performed under conditions favorable to both mother and child.

TYPES OF ASPHYXIA IN THE NEWBORN

Asphyxia of every kind and degree is finally due to a single cause: deficiency of oxygen. Apart from the depression induced by narcotics, four chief forms of asphyxia are seen in the newborn. In asphyxia livida the child is intensely cyanotic. The lips are blue, and the cutaneous veins are engorged. The umbilical cord is often found drawn tight around the baby's neck. All the signs indicate that for a brief time during delivery the passage of blood back and forth between the child and the placenta has been stopped or greatly impeded, or that the circulation to the head has been obstructed. The appearance is much like the first, or "plum-colored" stage seen in cases of pulmonary edema induced by one of the war gases. Livid babies that are not deeply narcotized, and in which the heart is still beating strongly, are generally resuscitated readily by inhalation. The duration and intensity of asphyxia have not been sufficient to induce a dangerous degree of depression of the circulation or of the respiratory and tonic centers in the nervous system.

Far more serious is asphyxia pallida. In this condition the capillaries and veins of the skin are empty: indicating a failure of the circulation. The heart beats slowly and feebly, if at all. As Eastman has emphasized, the child is virtually in a state of shock resulting usually from a prolonged delivery, with obstruction of the umbilical vessels, and intense asphyxia. Respiration is profoundly depressed. But even more serious is the absence of muscle tonus, because of the depression of the centers in the nervous system that normally induce this state throughout the body. Because of the flaccidity of the musculature the blood stagnates in the tissues, the venous return is insufficient to supply the heart, and the circulation sinks toward complete failure. As the vasomotor nervous system is not involved, there is no

reason to expect adrenalin and related drugs to be helpful; and they are not.

A third form of asphyxia which, unlike those above described, develops after birth, results when compression of the head during delivery has induced an intracranial hemorrhage. In such cases the child may breathe at birth and for a time thereafter; but as the seepage of blood from the ruptured vessels gradually compresses the medullary centers and diminishes their blood supply, deprivation of oxygen develops. The sensitivity of the respiratory center to carbon dioxide is correspondingly diminished and the breathing gradually fails.

A fourth and related form of asphyxia occurs when obstruction of the fetal circulation during delivery has induced premature gasps. Such gasps may draw meconium and other detritus into the trachea and bronchi and obstruct the initial efforts of the child to breathe. Clearing of the trachea by means of an aspiratory sound or by "milking" is then of prime importance. As it has been suggested that administration of carbon dioxide might cause the material to be drawn deeper, it must be pointed out that the sooner the airways are expanded, along with all other parts of the lungs, the sooner the mucosal cilia will clear them.

Bufe estimates that of the infants that die in the first day approximately a quarter succumb because of intracranial hemorrhage, and a quarter because of obstruction of airways by aspirated material. Doubtless many others succeed in overcoming each of these initial handicaps and become normal children.

It is noteworthy that asphyxia livida and asphyxia pallida are developed before delivery. On the other hand, the asphyxias due to intracranial hemorrhage, narcotic drugs, and inspiration of meconium, although initiated during birth, develop mainly after birth.

THE NARCOTIZED BABY

One of the commonest causes of apnea in the newborn at the present time in America is the excessive use—or misuse—of narcotics and hypnotics to ease the pains of labor. In varying degrees all such drugs are respiratory depressants. When administered to the mother they diffuse readily from the maternal to the fetal circulation. And with equal amounts of narcotics in the two bloods, the baby is much the more strongly affected. During the early stages of labor this is of no importance; for the fetal respiratory exchange is still effected through the placenta. But a dosage that at the time of delivery merely quiets the mother without appreciably depressing her respiration, may render the infant so apneic and lethargic after birth that measures of resuscitation are necessary.

The hazard of loss of infant life from the administration of large doses of morphine to the mother late in labor has long been recognized. Morphine decreases the sensitivity of the respiratory center to its normal stimulus, carbon dioxide, in the newborn much more than it does in the adult. I have seen an otherwise normal baby, born of a heavily morphinized, but still breathing, mother that would not breathe at all on any stimulus less than an inhalation of 20 per cent of carbon dioxide; and then too feebly to survive. Irving reports that less than 2 per cent of all normal babies born of undrugged mothers fail to breathe immediately at birth. In other words, 98 per cent of normal undrugged babies begin to breathe in the first of the two ways described in the preceding chapter. But under some of the narcotics and hypnotics now commonly used, the percentage of initial nonbreathers rises ten fold or even twenty fold. Many are now narcotized or asphyxiated to such a degree as to begin breathing only with gasps. Under the best hospital conditions

most of these apneic and gasping infants are successfully resuscitated. But under the less advantageous conditions of home delivery, many a deeply narcotized baby never breathes, or lives for only a few hours.

In the recent study by Bundeson and his associates of the Chicago Board of Health it was found that more than half the cases in which such drugs as morphine, scopolamine and the barbiturates were used, the babies were born in a deeply narcotized condition. In some cases respiration was established with great difficulty. Others died without emerging from their narcotized and asphyxiated state. When only moderate doses were given, the effect on the child was nevertheless that of diminishing his chance for living. The peril to the child was found to be especially grave when large doses of analgesics were given to abolish the pains of labor, followed by administration of extract of posterior pituitary to incite or increase them.

When only moderate doses of morphine are given, and given only in the early stages of labor, the depressant effects of the drug have largely worn off before the baby is required to breathe for itself; and even if the baby is still slightly narcotized, carbon dioxide can generally be relied on to stimulate it to breathe. But the antidotal action of carbon dioxide against the effects of some of the barbiturates is much less effective. For this reason the use of the barbiturates in obstetrics should be confined to those members of this group of drugs whose action is comparatively brief (2 or 3 hours), and the dosage should be such that the effect of the narcotic is virtually ended (to be replaced by an anesthetic) before the last stages of labor, after which the baby is required to breathe for itself.

The drugs classed as narcotics, analgesics, hypnotics, and anesthetics, differ widely from each other in three main features.

With some, the anesthetic effect is gone in a few seconds: as with nitrous oxide and ethylene. With others it lasts on for many minutes, as with ether and chloroform. With yet others it passes off in two or three, or at most, four or five hours: as with codein and morphine. With still others the narcosis may still be deep after 10 or 12 hours or more; and this is particularly the case with some of the barbiturates. Obviously if the baby is not to be born narcotized, drugs of prolonged effect should be administered only early in labor and only those of brief effect employed in the terminal stages. Even when a drugged baby breathes, it breathes weakly; and its liability to a continuance of atelectatic areas in its lungs and the development of pneumonia is much greater than in the normal child.

The second feature in which these drugs differ is their capacity to induce unconsciousness of acute pain. Some are anesthetics, others merely narcotics. Narcotics and hypnotics should be used only early in labor: anesthetics only late in labor.

The third feature, that in varying degree renders various drugs suitable, or unsuitable, for use in labor, lies in their influence on respiration. Most of the volatile anesthetics, if administered in moderate amounts, tend to induce some degree of overbreathing, and become depressants only when administered in excess. Most of the narcotics, on the contrary, are respiratory depressants even in small dosage, and in large dosage bring respiration to a stop. With some of the latter, e.g. morphine—the effects are due merely to a decrease in the sensitivity of the respiratory center to its normal stimulus. If the narcosis is only moderately deep, it may be counteracted by concentrations of carbon dioxide above the normal. With others—notably the barbiturates—the abolition of sensitivity to carbon dioxide is so marked that some investigators who have used

these drugs on animals, as well as some obstetricians who have administered them to women, have even been led to doubt whether carbon dioxide really plays a major part in the regulation of breathing. In deep barbiturate narcosis the responsiveness of the respiratory center to its normal stimulus is in fact so nearly abolished that breathing continues mainly under the influence of anoxia. Experiments on animals by Marshall and Rosenfeld have shown that the administration of oxygen by removing this influence may even induce a fatal apnea.

A recent study of various hypnotics in labor led Irving and his collaborators to "believe that morphine or any of its derivatives has no place during labor as they distinctly delay the initial respirations of the child." On the contrary, the use of considerable dosages of the barbiturates, at least in hospitals, was approved. Yet neither experimental nor clinical evidence seems to justify a belief that for a given degree of protection of the mother from suffering the barbiturates are much less depressant of respiration in the child than is morphine. The safe rule would be that sedatives should not be administered in excess of the amount required to relieve anxiety. The behavior of the infant is the best test of safe practice. Normally its respiration develops as an increase of the respiratory movements of the fetus supported by the development also of sufficient tonus to retain each increment of lung expansion as it is gained. If, on the contrary, any considerable percentage of normally born infants begin to breathe only after an apnea and asphyxial gasps, as many now do, the drugging of the mothers is excessive.

As nitrous oxide is one of the anesthetics now commonly used in labor, attention should be drawn to Eastman's warning that the amount of oxygen administered with the gas should be kept above 15 per cent, and that if it falls to 10 per cent or less, a

marked degree of fetal anoxemia may be produced, and profound asphyxia may result. Neglect of this general precaution in surgical operations under nitrous oxide has recently been shown by Courville to result in some cases in nervous sequelae and deaths essentially like those following prolonged carbon monoxide asphyxia.

The properties of drugs desirable for use in obstetrics are in many respects different from those desirable for surgical operations. In both fields the prevention of suffering should be as complete as possible without inducing damage. But the surgeon deals only with a single patient; the obstetrician with two. And the fact is now too often overlooked that the science of pharmacology affords no means of rendering childbirth free from even the slightest discomfort or recollection in the mother, except at the price of an occasional infant life.

Chapter XI

RESUSCITATION OF THE NEWBORN

IN THE resuscitation of the newborn the aim should not be to maintain a prolonged artificial respiration; the aim should be to introduce a sustaining and stimulating gas mixture into the lungs, and thereby to induce tonus and natural breathing at the earliest possible moment.

Much of common belief and practice in regard to manual artificial respiration is unsound or even absurd. Compressing the thorax of an apneic baby in which the lungs are still completely atelectatic cannot draw air into them. Even after the lungs have been distended manual artificial respiration can induce only expiration. Inspiration is produced only by the elastic recoil of the chest due to such tonus as the muscles may have. No squeezing, pulling, or stretching of the body or limbs can induce the slightest inflation of its lungs, although Schultze's method of swinging the apneic and atelectatic baby, or the safer method of moving the body feetward and then sharply headward, may jerk the lungs partially open. If any other form of handling induces breathing, that result is induced reflexly, not mechanically.

Mechanical devices for artificial respiration will be discussed in chapter XVII. Here it is enough to say that even when they induce a movement of air in and out of the lungs, they have the defect of aiming to do for the child what it should be stimulated to do for itself. On this account the Drinker apparatus, valuable in other conditions, is not generally advantageous in resuscitation of the newborn. To such devices as the pulmometer, so-called resuscitators and other apparatus of their type, there is

the decisive objection that they apply negative pressure to the lungs and thus tend to maintain, or again to induce, atelectasis. How little the subject of resuscitation is understood is indicated by the fact that such devices still are sold. And absurdly it is the demonstration of the capacity of these devices to suck a rubber bag flat that induces hospital authorities to buy them. Yet the worst possible treatment of an asphyxial baby is to deflate its lungs.

Two other modes of resuscitation are known. Their features are well illustrated by the analogy, suggested in the preceding chapter, between an asphyxial infant and a stalled motor car. One mode of resuscitation—not yet entirely eliminated—involves strong, even painful, afferent stimulation. The apneic infant is plunged into cold water; or it is slapped and kneaded. The large finger of the obstetrician is thrust into the tiny anus of the infant. Like a badly adjusted motor it is “cranked” so vigorously that, if there is any vitality, a gasp results.

The other mode of resuscitation was for many centuries exemplified only by mouth to mouth insufflation. Now it has been developed into the inhalation of a mixture of oxygen and carbon dioxide. It aims, not to excite a gasp, but to restore a nearly normal adjustment of the organism, particularly a normal influence of oxygen and carbon dioxide upon the respiratory and tonic centers in the nervous system. And the success of this mode of resuscitation indicates that it is more important to aim at restoration of normal adjustment of the elements of vitality than to try to excite a reflex gasp.

INHALATION AND INSUFFLATION

For all moderate cases of asphyxia, it is sufficient to administer the mixture of oxygen and carbon dioxide merely by inhalation. After the mouth and pharynx—and if necessary the trachea

also—have been cleared, a close-fitting mask is held tight over the face and a small rubber bag, attached to the mask and filled with a mixture of oxygen and carbon dioxide, is squeezed 10 or 15 times a minute. Usually a small, but sufficient, part of the lungs is thus inflated; and under the influence of the inhaled gases the baby begins to breathe. The administration of the gas is then continued by allowing the baby to rebreathe into the bag; and respiration soon becomes vigorous. Simultaneously and equally important, the centers in the spinal cord—now relieved of anoxia and stimulated by carbon dioxide—induce an increasing degree of tonus in the musculature of the baby. The thorax and lungs are thereby dilated; and the tonic intratissue and intra-abdominal pressures send a full supply of blood to the right heart. And with this support the heart action and circulation become strong.

For cases of profound asphyxia, in which the baby is entirely flaccid and its glottis relaxed, the mixture of gases should be administered by insufflation by the Meltzer-Flagg technique through a sound inserted down the trachea almost to the bronchi. Whether or not any considerable degree of direct inflation of the lungs can be, or should be, thus induced is doubtful; for Wilson has shown that forcible inflation may injure the lungs. A moderate intrabronchial positive pressure—not to exceed 25 or 30 mm. of mercury, or 35 to 50 cm. of water—may help to dilate adjacent areas of the lungs. But the chief effect is physiological rather than mechanical. If the heart is still beating, the influence of the insufflated gases generally induces a sufficient degree of tonus in the respiratory muscles for them to produce a gradual expansion of the thorax and inflation of the lungs. And in acute asphyxia the aid to the circulation through an increased venous return is even more important.

In some hospitals in Germany and England carbon dioxide

is used without oxygen. A rubber bag is filled with the gas and a small catheter is inserted in one nostril. The sharp smarting induced in the nose by pure carbon dioxide excites a reflex gasp; and once breathing has started the gas entering the one nostril is diluted by the air inhaled through the mouth and the other nostril. This technique is effective, but a little harsh and, I think, not entirely safe.

Intracardiac injection of adrenalin is not beneficial for the moribund; and a hole punched in the heart may be seriously harmful for the living. Intravenous injection of lobelin and related drugs may induce gasps; but such drugs may be otherwise harmful.

THE VALUE OF OXYGEN

Oxygen, as the word is here used, has two somewhat different meanings. By oxygen we may mean that component of the air that is absorbed into the blood in the lungs, carried to the tissues, and there consumed in the vital combustion. In this sense oxygen is the most immediately essential of all tissue foodstuffs. The restoration of a full supply of oxygen to the tissues, and particularly to the centers in the nervous system, is the main element in resuscitation from asphyxia.

By oxygen we may also mean the compressed gas that is bought in cylinders and administered by means of a mask. In this sense oxygen is not essential for resuscitation; it is merely a convenience. In many conditions its administration is very slightly more beneficial than mere air. For this there are three principal reasons. One of these reasons lies in the chemical character of hemoglobin, which gives this substance so high an affinity for oxygen that it is almost completely saturated (98 per cent) even by the normal oxygen pressure (14 or 15 per cent)

in the air of the lungs. A second reason is that oxygen has only a low solubility in the blood plasma; and an increased pressure of the gas within practical limits does not add very materially to the amount that the blood can carry. The third and most important reason arises from the fact that, except during deep breathing, only a small fraction of the lung air is exchanged for fresh air at each breath; and this fraction is further decreased during respiratory depression. For all of these reasons the blood passing through the lungs will carry away to the tissues only 5 or 10 per cent more oxygen when the pure gas is breathed instead of mere air.

Except under such conditions as those of pneumonia, in which a large part of the lungs may be out of action, but the remainder is well ventilated, an increase in the percentage of oxygen inhaled is therefore of no great advantage without an increase also in the volume of the breathing and of the circulation as well; and such increase oxygen alone does not induce. This is true of a normal man or baby, and it is equally true, and even more important, under such profound functional depressions as occur in the victims of asphyxia.

A cyanotic baby receiving pure oxygen may continue cyanotic. The same baby receiving carbon dioxide in air soon breathes deeply and grows pink.

THE INTERACTIONS OF CARBON DIOXIDE AND OXYGEN

Carbon dioxide is a highly soluble and readily diffusible gas. The amount produced in the tissues normally determines the volume of breathing. In states of depression the decreased production of carbon dioxide involves a corresponding decrease in respiration. If the amount of carbon dioxide in the arterial blood is diminished, the motor centers in the nervous system are

affected; muscle tonus is lowered, and less carbon dioxide is produced. These effects, one upon another, constitute a vicious circle.

The amount of carbon dioxide carried in simple solution in the arterial blood is directly proportional to the concentration (partial pressure) of that gas in the lungs. And normally this concentration is 5 per cent or a little more. Proportional to the amount in solution also is the stimulating action upon the respiratory and other motor centers that control muscular tonus.

The last statement in regard to carbon dioxide is, however, strictly true only under normal resting conditions. Under abnormal conditions, such as those of asphyxia, or even after vigorous muscular exercise, another factor plays an important part: namely the sensitivity of the respiratory center. The effect of a given amount of carbon dioxide upon respiration is determined by the sensitivity of the respiratory center at the time. And among the influences that determine the sensitivity of the respiratory center one of the most important is oxygen. It is only because of the constancy of the supply of oxygen under all normal conditions, and the consequent uniform sensitivity of the respiratory center, that carbon dioxide appears to be the prime controller of the volume of breathing. In all the stages of the development of asphyxia and of recovery from asphyxia the sensitivity of the respiratory center is a vitally important element. If the sensitivity is decreased to half of normal, a normal amount of carbon dioxide will induce only half the normal volume of breathing; and under this condition twice the normal amount of carbon dioxide is required to induce a normal volume of breathing.

A variation from the normal amount of oxygen may affect respiration in two opposite ways according to its degree. Within moderate limits, a decrease of oxygen induces an increased sensi-

tivity to carbon dioxide and thus an increase of breathing for a given amount of carbon dioxide produced in the body. Beyond this point the effect of a decreasing supply of oxygen is reversed; and the respiratory center becomes so much depressed that even with the same production of carbon dioxide the volume of breathing decreases. Because of the decrease of respiration the supply of oxygen to the tissues also decreases. In this way the sensitivity of the center and the volume of breathing are progressively decreased still further. To combat this depression the prime means that nature and science afford is the inhalation of carbon dioxide in amounts sufficiently more than normal to induce a nearly normal volume of breathing. For practical purposes, and theoretical as well, the most important distinction between carbon dioxide and oxygen lies in the fact that while carbon dioxide acts upon respiration rapidly, so that breathing may be doubled or trebled in a few seconds; any alteration in the supply of oxygen, on the contrary, usually affects the sensitivity of the respiratory center and the volume of breathing only slowly. Yet it is also true that, if pure oxygen is suddenly administered to a man who has been hyperpneic in the early stages of asphyxia, respiration may fail entirely. This is the "oxygen apnea" described many years ago by Mosso, and referred to in a previous chapter. Such an apnea does not occur if even a small amount of carbon dioxide is mixed with the oxygen. Within certain limits an increase of carbon dioxide may compensate for a deficiency of oxygen. Of this relation there are many practical examples. Coal miners and city firemen often fall unconscious when they come out of smoke and inhale fresh air. Experimentally Gellhorn has recently shown that normal men who are made to breathe only 9 per cent of oxygen without carbon dioxide become confused and unable to control their hands, or to write legibly; but

that if 3 per cent of carbon dioxide is added, they remain quite normal on the same low supply of oxygen.

Finally, among the interactions of oxygen and carbon dioxide, one of the most important is that in which the two gases act upon hemoglobin. Although hemoglobin is not directly the vehicle by which carbon dioxide is transported in the blood, the amount of carbon dioxide present strongly affects the affinity of hemoglobin for oxygen. If the concentration of carbon dioxide is high the oxygen is readily given off by the blood as it passes through the tissues. If, however, the blood is markedly acapnial, its hemoglobin parts with its oxygen much less readily. The tissues may then remain hungry for oxygen in the presence of plenty, until under inhalation of carbon dioxide the blood is influenced to part with the life-giving oxygen that it carries.

For all of these reasons carbon dioxide strengthens the capacity of the organism to withstand anoxia. In proper dilution whether in oxygen or even merely in air, carbon dioxide is a far more effective agent for resuscitation from asphyxia than is pure oxygen. Miescher was speaking truth in more ways than were then known, when he wrote in his classic discussion of the control of breathing: "Over the oxygen supply of the body carbon dioxide spreads its protecting wings."

OBJECTIONS TO THE USE OF CARBON DIOXIDE

Three objections have been offered to the use of carbon dioxide with oxygen for the newborn. One is that some babies do not respond to the stimulus of 5 per cent carbon dioxide. The answer is that this is generally true only of those born in deep narcosis, and that in proportion as the sensitivity of the respiratory center is depressed by drugs or by asphyxia, higher percentages of carbon dioxide are needed to induce stimulation of breathing and muscle tonus.

A second objection is that the newborn, unlike the victims of carbon monoxide, have no foreign gas to be ventilated out of the blood. The answer is that in both of these forms of asphyxia carbon dioxide is needed to stimulate tonus and support the circulation, quite as much as it is needed to stimulate respiration.

A third objection is that raised by Eastman on the basis of his extremely careful and valuable studies upon asphyxia neonatorum. In cases of asphyxia pallida he finds in the blood low oxygen, low pH, low alkali, high lactic acid and a more than normal pressure of carbon dioxide. He accepts the view that such conditions constitute an "acidosis" in the sense of an acid intoxication; and he infers that administration of carbon dioxide should exacerbate the intoxication. The answer is that some years ago the same objection, based on the present teaching of biochemistry, was urged by others against the administration of carbon dioxide to patients who are "acidotic" after anesthesia; and that it is still urged by a few writers against the administration of carbon dioxide to the victims of carbon monoxide asphyxia.

Since the introduction of this treatment a few years ago inhalations of carbon dioxide have been administered to many thousands of asphyxial babies, adult victims of carbon monoxide poisoning and patients emerging from anesthesia after major surgical operations. The blood in all such cases is in essentially the condition that biochemists regard as acute "acidosis." Yet up to the present time there has not been reported a single case of such ill effects as an "exacerbation of acidosis" might be expected to induce. Experience has shown, on the contrary, that beside its other benefits, inhalation of carbon dioxide tends to relieve "acidosis" by recalling alkali to the blood. And, as the sum total of all the evidence presented in this book demonstrates,

asphyxia does not induce "acidosis," if by that term is meant a true acid poisoning.

THE PREVENTION OF NEONATAL DEATHS

In the preceding chapter it was emphasized that the mortality of the neonatal period—the first few weeks of life—is nearly, or quite, as high as that of the birth period itself. The causes of the large majority of the deaths in this period, especially among premature babies, are incomplete expansion of the lungs and its consequences—recurring anoxia and pneumonia.

The course of events in a typical case is as follows: The child breathes at birth, but not with such vigor as to induce more than a partial expansion of its lungs. In the hours and days thereafter its low metabolism and low heat production involve a low production of carbon dioxide. Its breathing is constantly weak. From time to time it has spells of respiratory depression in which the ventilation of the lungs is so poor that serious anoxia develops. The child becomes cyanotic. If it has sufficient vitality, the anoxia increases the sensitivity of the respiratory center sufficiently to balance the subnormal stimulus of insufficient carbon dioxide. In that case respiration improves and life continues. Finally, however, there comes a time in which the anoxia is so acute that the sensitivity of the center is depressed and respiration fails.

If atelectasis persists into the second or third week, pneumonia commonly develops. Cruikshank in his celebrated series of autopsies found that among 800 infants that had died in the neonatal period, there were 197 cases of pneumonia; 60 during the first week, 87 in the second, 37 in the third and 13 in the fourth. If deaths from asphyxia, prematurity and atelectasis were excluded, the frequency of pneumonia was practically 2 in 3. The

Chicago report, previously referred to, is to this same general effect. Van Reuss has summarized the evidence of German observers in the statements: that the expansion of the lung is longer delayed in debilitated and premature infants; and that pneumonia is apt to supervene in the atelectatic lungs of premature infants. He advises that the treatment of atelectasis should be directed toward expanding the lungs by stimulating deep respiration.

Yet until recently the therapy commonly employed to combat a continuance of atelectasis consisted of little more than stinging the soles of the feet with a rubber band or some other means of making the child cry, keeping it warm in an incubator, and administering oxygen. The ineffectiveness of this treatment is demonstrated by the high mortality of babies suffering from a continuance of atelectasis.

Far more effective is the inhalation of carbon dioxide, either mixed with oxygen and administered by means of a mask, or with air and administered by means of a small tent, into which the gas is passed, under accurate control by a needle valve, through an injector in the top of the tent. It is thus mixed with the air which it draws with it through the injector to a concentration of 3 to 6 per cent, as the response of the child may indicate to be needed. This injector tent is described in a later chapter. Under such a tent respiration begins to improve almost immediately, and soon becomes deep and full, although the rate should not be increased. Cyanosis is replaced by a bright pink color; and all signs indicate a marked improvement in the circulation. The inhalation is continued for 10 or 15 minutes and repeated three or four times a day, or as needed, until the lungs are fully dilated, and the general vitality of the child becomes normal.

A decisive demonstration of the life saving value of the inhalational treatment of premature infants was afforded by Dr. A. R. Dafoe's success with the Dionne quintuplets; the first such multiple births to survive the neonatal period.

INHALATION IN CASES OF INTRACRANIAL HEMORRHAGE

Beside its demonstrated benefits in cases of continued atelectasis, there is also reason to expect that this treatment may prevent respiratory failure in some cases of intracranial hemorrhage. White, by administering essentially the same treatment to cases of intracranial hemorrhage in adults, was sometimes able to save life.

The amount of carbon dioxide which should be administered in all the various degrees of narcosis and asphyxia can be defined only as that percentage which in each case is required to induce breathing. In cases of slight asphyxia 5 per cent is generally sufficient; in cases of profound narcosis and asphyxia 10 per cent, or even higher concentrations, may be requisite at first. But as soon as respiration is initiated, the strong mixture should be replaced by that of 5 per cent carbon dioxide in 95 per cent oxygen.

DEVELOPMENT OF THE INHALATIONAL TREATMENT

In 1925 the time was ripe for the application of inhalational resuscitation to the newborn. If it had not come in one way, it would have come in another. Actually it came in several different ways in different countries.

It was twenty years since Haldane had shown the part that carbon dioxide plays in breathing; and fifteen years since I had started to introduce that gas into the surgical operating room. But it was still unknown in the obstetrical delivery room.

In November of that year, 1925, I was lecturing in England on the use of carbon dioxide in connection with anesthesia and its value as a resuscitant in carbon monoxide asphyxia. Both were still very radical ideas. They were so radical that after I had finished my lectures in London and had gone to repeat them in other cities, the anesthetists called another meeting. And to that meeting they invited Haldane to come and tell them whether there was any truth in the idea that during and after anesthesia respiration can be controlled with carbon dioxide. He resolved their doubts.

Meanwhile in a hospital at Manchester I saw a ward where babies suffering from malnutrition were being treated, under the supervision of Prof. H. S. Raper, in incubators ventilated with air plus a considerable addition of oxygen, or a small addition of carbon dioxide. Both gases were beneficial. The object was nutritional, not respiratory; but to me the benefits of this treatment were suggestive for its extension to the newborn. Up to that time I had supposed, as everyone then did, that the blood of an asphyxial baby must already contain an excess of carbon dioxide. And I had not dared to administer more.

Later that autumn, as the guest of Prof. Winifred Cullis, I worked in the physiological laboratory of the Women's Medical College, London, and discussed the respiration and asphyxia of the newborn with her and her colleague, Dr. (now Dame) Louise McIlroy, professor of obstetrics in that school and the Royal Free Hospital. And there, early in 1926, for the first time in Europe a mixture of carbon dioxide and oxygen was put into regular use by Dr. McIlroy for resuscitation of the newborn.

In America a less orthodox development had already begun. In several cities physicians who had seen the resuscitation of cases of carbon monoxide asphyxia, and who were later faced

with an asphyxial baby, called in the rescue crews of the fire department with their inhalators; and generally the baby was resuscitated. For some years even the largest hospitals also invoked this new service of the fire department. Then in one hospital after another—particularly after mistakes over the telephone had brought the whole fire department to the hospital—cylinders of carbon dioxide and oxygen and suitable inhalators gradually became a regular part of the equipment of obstetrical delivery rooms.

In Germany the course of events was again different. Soon after the inhalational method of resuscitation was introduced in America it was adopted also in Germany for the treatment of carbon monoxide asphyxia. In surgery the use of carbon dioxide was introduced about 1927 by Prof. A. W. Meyer, surgical director at the Westend Hospital in Berlin-Charlottenburg. He was the son of the eminent pharmacologist, Prof. Hans Horst Meyer of Vienna under whom I had studied many years before, and to whom I had always sent copies of my papers. Professor Meyer had forwarded those dealing with the use of carbon dioxide in anesthesia to his son in Berlin. From surgery and anesthesia the use of carbon dioxide passed to obstetrics.

Now (1938) the last traces of the old beliefs that carbon dioxide is only an “asphyxiant gas,” and that it “exacerbates acidosis” are fading out; and many confirmations of the safety and effectiveness of inhalational resuscitation have been published: among others by McGrath and Kuder, Moncreef, Blaikley and Gibberd, Bauer, Lloyd-Williams and Wilson, Torrey and Johnson.

Chapter XII

POSTOPERATIVE DEPRESSION

NO FEATURE of illness is more common than that of muscular weakness. Yet of none has the significance been more generally overlooked. The patient, who only an hour ago emerged from anesthesia after a major surgical operation, exhibits a striking contrast to the same person when in a state of vigorous health. In the one condition the muscles are not only weak but flaccid; in the other they are both strong and elastic.

Even after the less exhausting experience of such a disease as influenza, the muscles of the body may afford too little power and support to permit a man to walk erect, or to stand, or to sit up in bed, or, in extreme cases, even to lift his head from the pillow. In such prostrations the muscles of speech are so weak that his voice sinks to a whisper. In the great epidemic of influenza in 1918 thousands died; most of them of pneumonia consequent on prostration; many of sheer prostration. But how prostration (*Lebenschwäche*) leads to pneumonia, or how prostration alone may induce death, has not been explained.

In this chapter we shall consider the seat and some of the causes of this muscular weakness. We shall find its seat in the motor centers of the spinal cord; and its immediate cause in the failure of these centers to induce in the muscles the continuous, gentle, elastic pull of tonus. We shall see how this explanation of weakness in the muscles of the legs and back holds true also of those involved in respiration. Then we shall trace the causal relation between the depression of tonus in the respiratory muscles and the development of postoperative pulmonary complica-

tions, particularly atelectasis. When the respiratory muscles are relaxed the size of the thorax shrinks, the airways are occluded, and the lungs are deflated. In the next chapter we shall see that occlusion of the airways—by preventing the normal drainage of the lungs—may play a critical part in the development of pneumonia. And in the chapter after that the lowered muscular tonus after operations and illness will be shown to be a principal factor in depression of the circulation and in surgical shock.

POSTURE IN STANDING AND BREATHING

Posture, particularly the ability to stand erect or to hold one's head up, is dependent upon the tonus of the muscles of the legs, back and neck. This is recognized by all. But little recognized is another feature of posture and its equally essential dependence upon tonus. That feature is the continuous holding of the thorax in a degree of expansion that during health keeps the lungs at all times well inflated. Just as the erect position shows the action of the muscles that support the head, so the large volume of the stationary air that is normally held in the lungs shows the action of the respiratory muscles in the lifelong posture of the thorax.

The outstanding feature of both these forms of posture is that they are maintained indefinitely without exertion of the will and also without fatigue. If voluntary contractions of the muscles were required, they would soon be as tired as those in the shoulder when a penny is held at arm's length until the hand drops. In tonic contraction the metabolism is low; the reparative processes, for which the circulation supplies the material and removes the waste, fully balance the combustion. In all other respects tonic contraction and active contraction are identical.

Nevertheless the amount of combustion due to the tonus of all the muscles in the body is a considerable element in the basal metabolism and in the so-called chemical control of body temperature. The metabolism of muscles in tonus has therefore two general influences. It contributes to keeping the body warm; and as the muscles produce carbon dioxide in proportion to their tonus, tonus thus largely determines the volume of air that is breathed. In addition tonus keeps the lungs expanded and insures the venous return of the blood to the right heart.

THE CONTROL OF TONIC ELASTICITY

Ordinarily tonus is a function of which we are entirely unaware in ourselves, and which we fail to notice in others. It is only when we are cold, or developing a fever, or under certain emotions, that tonus impresses itself upon us. Then tonus is so much intensified that the muscles of the limbs twitch, those of the jaws cause the teeth to chatter, and the whole body falls into shivering.

We find in ourselves the ability to move each muscle gently, or forcibly, or very powerfully; and this experience inclines us to suppose that the impulses over nerve fibers and the contractions of muscle fibers must be effected in similar gradations. Experimental evidence indicates, however, that such is not the case. A weak contraction of a muscle is due to impulses over only a few nerve fibers, and to contraction by correspondingly few muscle fibers; but the impulses over each of these nerve fibers and the contractions of each of these muscle fibers are maximal. A stronger contraction of a muscle is due to a more rapid succession of impulses over a greater number of nerve fibers and involves the contraction of a greater number of muscle fibers. Only in a very powerful contraction do all the fibers in a motor nerve and

all the fibers in a muscle come into action simultaneously. This conception is true also of tonus. This form of contraction also at each instant involves only a few fibers. A few contract at one instant; then an instant later these relax and as many others contract; and so on in continual rotation of activity and rest. Strange as this seems, it is demonstrated decisively by observations on the electrical changes in a tonic muscle such as those of Barcroft and Barron, using Adrian's method, mentioned in chapter IX.

This continual play of contraction and relaxation among the fibers of a muscle is like that, brilliantly demonstrated by Krogh, which occurs among the blood capillaries that ramify among the fibers of a muscle. These minute vessels also are continually contracting and relaxing. At one moment a few capillaries are open, but the rest are closed. Then another group open and the first group close. It may well be that the capillaries that at any instant are opened are those around the muscle fibers which at that instant are active. If properly timed such a relation would form a sort of venous pump. But there is as yet no direct evidence for such coordination.

The gentle constant pull of a muscle in tonus is perhaps best described as elasticity. Yet it is an elasticity quite unlike the elasticity of a rubber band or a steel spring. It disappears the instant that the nerve to the muscle is severed. It is essentially a reflex in which the appearance of mere mechanical elasticity is imitated by the distributed contractions, now more, now fewer, of the fibers of the muscles.

As an illustration of tonic elasticity: I recently saw a little five year old girl in blooming health skipping along the pavement in an elastic and graceful dance. As she came down on each toe, the muscles of that leg appeared to bounce her up

again as if she were treading on springs. Yet such was in the main certainly not the reality. Instead, each time she came down on an extended toe, there was reflexly induced an innervation of an increased number of fibers in the muscles of that leg; and it was their contraction, not mere mechanical elasticity, that caused her next spring upward and onward. The part that innervation played was strikingly seen two weeks later; for then, after three days in bed with a cold the elasticity of the skipping legs was far less than before. Tonus was lower.

Although it has been suggested that the sympathetic nervous system may influence muscle tonus, it is generally agreed that in the main tonus is induced by impulses over motor nerves from cells in the anterior horns of the grey matter in the spinal cord. Many influences normally play upon these centers; and the strength, or rather the number, of nervous impulses that these centers send out over the motor nerves to induce tonus in muscles is the resultant of all these influences. Among these influences are the innervations from the brain, both from the cerebrum and the cerebellum, by way of the spinal cord. They may be stimulating in character, but are more often inhibitory. Others are from the skin; for a cold bath or even a draft of air increases tonus; while warm, stagnant, moist air lowers tonus. Other influences come by way of the afferent nerve fibers from the muscles themselves. And, as we saw in babies in the last chapter, and shall see in adults later on, the oxygen and carbon dioxide contents of the blood exert at times, either directly or through the respiratory center, an almost dominating control.

Therapeutically the drug that more directly than any other increases the tonic activity of the spinal nerve centers and thus raises muscular tonus is strychnine. Strychnine is par excel-

lence a tonic. In the early stages of anesthesia under ether and similar agents muscular tonus is increased. The influence of the higher centers is shut off and the lower motor centers are freed from their inhibition. In the stages of full anesthesia, and especially in deep anesthesia, the motor centers themselves are affected; their nervous discharges are diminished; and tonus is greatly lessened. The muscles are to a large extent relaxed and nearly flaccid.

At death tonus ceases; all the muscles of the body relax; and their elasticity is abolished. Simultaneously the lungs are deflated. A man who floats in fresh water when alive, sinks in sea water when dead: indicating a loss of two or three, or more, liters of lung volume.

THE VOLUME AND MOVEMENT OF THE LUNGS

The lungs are peculiar organs in that they have little independent activity or self control. Their size is merely that of the cavity of the thorax; when they are removed from the body, they collapse. Yet even in these organs tonus probably plays a part. The lungs are permeated with non-striated muscle fibers; and from their structure we should almost expect them to exhibit contractions like the stomach or the bladder. Macklin's observations indicate that at least a part of the elasticity of the lungs is due to this muscular element. But, except in asthma, in which the airways are actively constricted by the muscle fibers in their walls, and in emphysema, in which the muscular element may perhaps lose its tonicity, little is known of any inherent activity in the lungs. They merely inflate and deflate as the chest expands and contracts. And the expansion and contraction of the chest is wholly controlled by the muscles of the thorax and abdomen, and above all by the diaphragm.

These muscles, even including the diaphragm, are all of the type that is called "voluntary"; every one of them can be contracted or relaxed by the will. Yet as Hess has clearly shown their movements in breathing have less the character of voluntary contraction than they have of alternations between higher and lower degrees of tonus; and this is particularly the case in the diaphragm. As has been pointed out in previous chapters, it is probable that from the first breath of life until after the last this muscle never for an instant loses all of its tonus.

THE ABSORPTION OF OCCLUDED AIR

How essential it is that the lungs shall always be kept expanded is demonstrated by the rapidity with which a lobe or even an entire lung may be deflated when any one of the airways is closed. Whenever this happens the air in the occluded part is absorbed into the blood with surprising rapidity and completeness. This absorption is not a vital reaction, but a purely physical process. It occurs in exactly the same way that air is absorbed from any other body cavity, such as the pleural cavity, into which air, or any other non-irritant gas, has been injected.

The explanation of how and why a lung is collapsed by absorption of its gaseous contents, whenever the airway to that lung or lobe is blocked, is exactly the same as the explanation of the reabsorption of the air from the pleural space and the consequent reinflation of a tuberculous lung that has been collapsed by pneumothorax. In both cases, as M. C. Henderson and I have shown, the absorption is due to the partial pressures of the gases concerned; and in neither case does blood pressure play any part whatever.

In brief, the physics of the process of absorption is as follows:

In the lungs, so long as they are in free connection with the outside air, the total pressure of all the gases, oxygen, carbon dioxide, nitrogen, and water vapor, is the same as that of the atmospheric pressure in the outside air. Very nearly the same gas pressures prevail in the arterial blood as it leaves the lungs. In the tissues oxygen is absorbed and carbon dioxide is produced in nearly equal amounts. But owing to the difference in the manner in which oxygen and carbon dioxide respectively are held in the blood, the pressure of oxygen in the venous blood is greatly decreased, while the pressure of carbon dioxide is only slightly increased. The sum of the pressures of these two gases in the venous blood is therefore very much less than the sum of their pressures in the arterial blood. The partial pressure of nitrogen is, however, the same in both arterial and venous blood.

Suppose now that a few hundred cubic centimeters of air are injected into any body space, such for instance as the abdomen. At first carbon dioxide is given off from the blood and the tissues to the occluded air and part of its oxygen is absorbed. But the gaseous equilibrium that is thus approached, although never reached, approximates the gas pressures in the venous blood rather than the arterial blood; and more oxygen is therefore absorbed from this air, than the carbon dioxide that diffuses into it. The volume of the air is thus decreased and, as atmospheric pressure bears upon the exterior of the abdomen and as the soft tissues yield easily to atmospheric pressure, the space is decreased. As a result the nitrogen of the occluded air is now contained in a smaller space than before, and its partial pressure, therefore, is raised above its original pressure and thus also above the pressure of nitrogen in the blood.

It is one of the fundamental laws of gases that each gas dif-

fuses according to its own partial pressure regardless of what other gases may be present. Accordingly, a part of the nitrogen in this space that we are considering diffuses into the blood; and the total volume of the occluded gases is thus further decreased. This brings the partial pressure of the oxygen and carbon dioxide in the diminished space again into relative excess above the pressures of these gases in the venous blood, into and from which they therefore diffuse further. And, as a result of the continual interaction of these processes, any air that is injected into the abdominal cavity, or the pleural cavity, or any other body cavity, is gradually absorbed under the influence of purely physical principles.

Similarly air that is occluded in a lung by a plug in a bronchus is gradually absorbed into the blood. And as it is absorbed, the lung is gradually collapsed under the pressure of the atmosphere bearing down through the trachea and bronchi into the other lung, and by elevation of the diaphragm by the pressure of the atmosphere upon the abdomen. This appears to be the complete explanation of why it is that a plug in a main bronchus results in collapse of the lung on that side, and an expansion of the other lung to fill part of the space.

POSTOPERATIVE ATELECTASIS AND MASSIVE COLLAPSE

When Sir James Barr first recognized massive collapse of a lung as a sequel of a surgical operation, thirty years ago, he came very close to the true explanation of its underlying cause; he assigned it to "paralysis of the diaphragm" and treated it successfully with "a course of respiratory gymnastics." And if we change the word paralysis to "depression of tonus" and extend this conception of loss of tonus to all the respiratory muscles, and indeed to all the muscles of the body, we have

before us the condition that underlies not only atelectasis and massive collapse, but also practically all of the other features of postoperative depression of functions.

In more recent observations upon patients after surgical operations, it has been found by a number of observers that the vital capacity—that is, the maximum volume of air that a patient can exhale—may be decreased by as much as 50 per cent. In this decrease it is evident that the relaxation of the diaphragm plays a critical part, for it may be relaxed to such an extent that in X-ray pictures its shadow is as much as 7 or 8 centimeters headward from its normal position. This is as far as, or farther than, the diaphragm moves under the deepest and most forcible voluntary expiration.

The sum and substance of all these observations is that, when the vitality is reduced, the tonus of all the muscles in the body is correspondingly diminished. In the thorax particularly the decrease of tonus results in such a diminution of the size of the chest cavity, and such a deflation of the lungs, that many minute deaerated areas are produced.

This condition in its simple uncomplicated form has been well termed “collapse without symptoms.” When it is looked for it has been found after more than 80 per cent of all laparotomies. It is always accompanied by shallow respiration and rapid pulse.

This condition is so common that it may almost be called a normal sequel of major surgical operations. Why, then, is massive collapse not more common than it is? Why does it occur in some cases and not in all? The reason for this is apparently one of pure chance. When the lungs have been for a time partially deflated by the lowered tonus of the diaphragm, it may happen that mucus accumulates in one or another of the

major airways until the passage is completely closed. In that part of the lung which is thus occluded, another development then sets in. The gases contained in the occluded lobe or lung are absorbed into the blood, and the lobe or lung in the course of time—generally a rather short time—is completely collapsed. As one lung collapses, it draws the mediastinum after it, and atmospheric pressure inflates the other lung. Hence massive collapse of one lung tends to expand the other.

This conception rests mainly on the brilliant investigations of Coryllos in which he demonstrated experimentally that the one condition determining the development of atelectasis in any considerable part of a lung is the complete closing of its airway. Confirmation of this conception from the clinical side is afforded by the experience of Chevalier Jackson which shows that removal of an occluding foreign body from a main airway by means of the bronchoscope is followed by the automatic reinflation of the collapsed lung. The finding by several investigators that after an abdominal operation, even without atelectasis, the size of the chest is always decreased, leaves only one gap in the story: namely, the question how it is decreased. And that gap is filled by the demonstration (to be more fully described in a later chapter) by Oughterson, Greenberg, Searle and myself, that low tonus is one of the ordinary sequelae of anesthesia and operation. (If the deflation of the lungs is so extreme that many minor bronchioles are closed, a massive collapse may result, even without the plugging of a main bronchus.)

ATELECTASIS AFTER SPINAL ANESTHESIA

The part that loss of tonus plays in the development of post-operative atelectasis is strikingly attested by recent experience

in regard to spinal anesthesia in many surgical clinics. This experience is as significant as it was unexpected. It shows that pulmonary complications are rather frequent sequelae of spinal anesthesia. They are in fact, as Rovenstine finds, quite as frequent after spinal as after inhalational anesthesia, and two and a half times as frequent when intercostal paralysis occurs as when there is no paralysis. Similarly with inhalational anesthesia the frequency and degree of pulmonary complications are proportional to the depth of anesthesia and relaxation. Oxygen is more readily absorbed than nitrogen; and atelectasis develops more rapidly when the patient has inhaled oxygen than when he has breathed only air.

Even the blocking of the afferent nerve fibers between the spinal cord and the muscles is sufficient to decrease tonus. When in addition the anesthetic that is injected into the spinal canal reaches, not only the afferent, but also the motor nerves, tonus is abolished. In extreme cases the respiratory muscles are for a time completely paralyzed. Inhalation of carbon dioxide is then, of course, wholly ineffective. Life can be saved only by intratracheal insufflation of oxygen. In less marked cases the decreased tonus of these muscles permits such a decrease in the volume of the chest that the lungs are partially deflated, some of the airways may be closed, and the lungs be deflated.

Spinal anesthesia is not administered to patients as an experiment; but if it were, none clearer could be framed. The atelectasis that it sometimes induces demonstrates that loss of tonus is the prime cause of postoperative pulmonary complications.

This experience with spinal anesthesia is equally significant in another matter. Until recently it was universally supposed that when pulmonary complications follow an inhalational an-

thesia, a direct irritation of the lungs must be the cause. Now this opinion is weakened, or eliminated, by the finding that such a hypothesis is no longer needed. Certainly under spinal anesthesia no direct irritation of the lungs can possibly occur. Yet all the effects once assigned to such irritation occur under spinal anesthesia and occur on the whole even oftener than under inhalational anesthesia. From these facts it is logical to infer that in reality the cause of postoperative atelectasis after any form of anesthesia, whether spinal or inhalational, is not irritation of the lungs, but diminished tonus in the respiratory muscles.

PREVENTION AND RELIEF OF ATELECTASIS

Once atelectasis has developed, its relief requires both the clearing of occluded airways and the restoration of tonus. Fortunately in the large majority of cases the spontaneous return of vitality effects both of these objects even without special treatment. Coughing, vomiting, turning from one side to the other, even a vigorous slap on the side of the collapsed lung, may loosen a soft plug of mucus. Only in extreme cases is the use of the bronchoscope necessary. With the clearing of the airways, the returning tonus of the diaphragm and other muscles reexpands the lung.

For the prevention of atelectasis it is of prime importance that the period during which tonus is depressed should be as short as possible. To this end, the sooner any volatile anesthetic is eliminated, the better. Nothing tends more strongly to the development of atelectasis than to leave a patient, who is deeply etherized, acapnic and cyanotic, to the slow elimination of the anesthetic. And for the purpose of hastening the elimination of the anesthetic, overcoming cyanosis, restoring

tonus in the respiratory muscles and expanding the lungs, the inhalation of carbon dioxide for a time after termination of anesthesia and repetition of the inhalation as needed are the well attested means: ending with carbon dioxide in air, not oxygen. (For inhalator, see page 283.)

The main reason for overcoming atelectasis, redilating the lungs, and opening their airways, as soon as possible, is that in any area that continues to be occluded the conditions are highly favorable to the rapid development of any pathogenic organisms that may be present. Until, in quite recent years, this relation came to be more or less clearly understood, each 240 major operations on the average, even in the best surgical clinics, cost at least one life from pneumonia.

Chapter XIII

THE FUNCTIONAL FACTOR IN PNEUMONIA

IN THE onset of lobar pneumonia the physical signs often resemble those of atelectasis—particularly the form of atelectasis termed massive collapse. The two conditions are, in fact, so much alike, that, as Osler and McCrae remark “in some cases the distinction is very difficult.” The similarity, although most striking at the onset of pneumonia, is not limited to any one stage of the disease. Osler and McCrae also note that “in children the signs of a foreign body in a bronchus may be mistaken for those of broncho-pneumonia.” In the course of nearly every form of pneumonia there are also features that resemble one or another of the various manifestations of atelectasis.

Yet, as pneumonia is due to infection, it is now regarded as an altogether different disease from the merely physiological and physical processes and conditions involved in atelectasis. And the more clearly atelectasis is understood, the stronger becomes the tendency to differentiate pneumonia. Atelectasis comes wholly under the care of surgeons, while pneumonia is generally assigned to the care of physicians. As the two diseases are supposed to have altogether different causations, so too they are supposed to require correspondingly different treatments.

The search for a means of preventing, curing, or ameliorating pneumonia is now generally directed toward combatting toxemia. But, in spite of a vast amount of work the results, as compared with those in other bacterial diseases, such as diphtheria, are as yet relatively meager. The mortality from pneu-

monia under the best conditions of serum treatment is scarcely reduced by 50 per cent.

This relatively slight progress in the cure of pneumonia is the more noteworthy in view of the fact that the problem has been attacked as actively as that of other diseases by many able investigators using the methods of bacteriology, serology and preventive medicine. Thus the idea suggests itself that pneumonia may involve some factor that is not concerned in the other diseases, and that is not to be wholly overcome by the methods effective against them.

The aim of this chapter will be to show that this little recognized but extremely important factor is prevention of drainage. It is a factor with which physicians are usually little concerned, and which they have therefore overlooked, or rejected, in pneumonia. On the other hand it is a factor of a type with which surgeons are familiar in numerous forms; they recognize its presence or absence as of critical importance in practically all conditions of infection. It consists in occlusion, lack of drainage and the resulting absorption of the products of bacterial action and the spreading of infection.

Granting then, that the pneumococci and other pathogenic organisms are the essential cause of pneumonia, and not mere loss of muscle tonus as in postoperative atelectasis, three points must here be demonstrated. They are:

First, that occlusion of airways and deflation of the lungs may occur in pneumonia;

Second, that when these conditions are prevented, pneumonia does not develop, even from virulent infection;

And third, that even when pneumonia has begun to develop, an early reopening of the airways, and reestablishment of drainage through them are followed by a rapid recovery from the disease.

The main evidence in support of the first two of these points is afforded by the work of Coryllos and Birnbaum. The crucial demonstration of the last point is afforded by the experiments, which Haggard and I performed in collaboration with them.

THE IMPORTANCE OF DRAINAGE

The lungs are normally among the best drained organs in the body. The bronchi bear the same relation to the lungs that the Eustachian tubes do to the middle ears, and that the various ducts and foramina opening into the nasal passages bear to the sinuses of the head. As infection commonly enters through these passages, the first effect is usually the development of a catarrhal condition that closes the passage and prevents drainage. Then follows otitis media, sinusitis or pneumonitis.

For the free drainage of the lungs, it is essential that the airways shall at all times be kept open. Accordingly Nature has provided the lungs with several protective devices and reactions to insure the patency of the airways. The most obvious is the cough reflex, by which irritating foreign bodies are removed. Less obvious, but more constantly acting, is the continual flow of secretion from the depths of the lungs outward, which is induced by the minute waving cilia on the mucosa lining the air tubes. In addition inspiration and expiration induce synchronous expansions and contractions of the air tubes and these movements are probably accompanied by peristaltic waves in the muscular elements in the walls of these tubes.

On the other hand there is some evidence that a constriction of the bronchi may be induced reflexly by a severe chilling of the skin. And Osler and McCrae note that "the explosive onset of pneumonia bears a certain resemblance to the anaphylactic

reaction," in which the bronchi and bronchioles are constricted almost or quite to occlusion.

It is a common clinical observation—although its full significance is not recognized—that epidemics of pneumonia are most common in barracks, jails, and schools, where the occupants are not only in close contact, but are also sedentary. In hospitals a patient in the next bed to one with pneumonia may take the disease, or two or three cases may follow in rapid succession in a ward; but as Osler noted it is very exceptional for nurses or doctors to be attacked. Resistance to infection is a complex of many factors; but the immunity of the doctors and nurses may lie largely in the mere mechanical fact that, as they are active, their lungs are cleared before the infection finds lodgment. In pneumonia patients frequent changes of position, which tend to dislodge plugs of mucus in the bronchi, are recognized as advantageous. Finally, it has been noted in a number of hospitals that the pneumonia patient, who in his delirium jumps out of bed and runs until he is captured and brought back, instead of being made worse, often makes a surprisingly rapid recovery.

With all these indications of occluded airways and the benefit derived from reopening them, it is indeed surprising that internists have been so indifferent, indeed so strongly opposed as have many, to the conception that atelectasis is an important factor in pneumonia. Yet the reason is clear. They picture pneumonia as the disease is revealed at autopsy. Seeing the lungs of patients that have died of pneumonia—organs as solid as liver—they unhesitatingly reject the suggestion that such lungs can be opened or cleared to any appreciable extent by deep breathing, or even by means of the bronchoscope. And in this, of course, they are entirely correct. If the promotion

of drainage is to be most beneficial in pneumonia it must be applied in the earliest stages of occlusion and long before consolidation has developed.

Pneumonia should be treated both with serum and with measures to deepen breathing and prevent or relieve atelectasis.

EXPERIMENTAL ATELECTASIS AND PNEUMONIA

The first to grasp this idea clearly was the surgeon, Coryllos. In collaboration with Birnbaum, he was performing experiments on simple atelectasis. For this purpose they had developed small rubber balloons that could be inserted in a bronchus of a dog and inflated so as to close that airway. They found that within a few hours the X-ray picture of the thorax showed that the air in the occluded lung had been absorbed. That lung was deflated, while the other lung was almost correspondingly dilated. At the same time the heart moved toward the deflated lung, and the diaphragm on that side was drawn or pressed upward. Comparison of these experimental observations with cases of massive collapse in patients, particularly after abdominal operations, showed close correspondence. Removal of the balloon in the bronchus was followed in a few hours by the spontaneous reinflation of the lungs: a result essentially like that which Chevalier Jackson and Lee had shown to occur in the relief of acute massive collapse in patients, when the bronchus was cleared by means of bronchoscopy. There was virtually complete concordance also with the earlier clinical observations of W. Pasteur in England and Lichtheim in Germany.

Coryllos was further struck by the similarity of the initial symptoms of patients, who after surgical operations developed a massive collapse of a lung, and those patients who following

mere exposure to a chill or after a cold develop pneumonia. Both conditions are commonly characterized by a sudden onset of pain, dyspnea, often cyanosis, elevation of temperature and accelerated pulse, dullness over the affected lung, displacement of the mediastinum to that side, and elevation of that half of the diaphragm. These facts suggested that as the initial step in the development of lobar pneumonia there occurs a closure of the airways by thick, sticky mucus, and that the closure is followed by deflation of the occluded areas of the lungs.

In opposition to this conception was the observation, which is commonly quoted in textbooks of medicine in the chapters on pneumonia, that at autopsy the infected lung is always found both heavier and larger than the sound lung. But, as Coryllos demonstrated, this objection is removed when the trachea is clamped before the thorax is opened. Then the difference in size is reversed; the pneumonic lung is much smaller than the sound lung. It is only when the clamp is removed, and the sound lung allowed to deflate, that the ordinary misleading appearance is again induced. The conclusion to be drawn from these observations is that atelectasis is always one of the initial stages in the development of pneumonia.

This opinion was then supported by experiments in which a true pneumonia was induced in dogs. For this purpose a virulent culture of pneumococci was introduced as deep as possible into one of the main bronchi in dogs. But, as dogs are extremely resistant to pneumonic infection, it was found that in order to induce pneumonia it was not enough merely to introduce the pathogenic organisms into the lung. It was essential also that the animals should be so deeply narcotized with a barbiturate that the cough reflex was entirely abolished, and respiration depressed. Under these conditions—but only so—

the dogs developed a unilateral lobar pneumonia entirely similar to that in human patients. This pneumonia then progressed through all the typical stages both clinical and pathological to an almost invariably fatal issue.

On this evidence Coryllos and Birnbaum very justly based the conclusions that in their initial stages lobar pneumonia is a "pneumococcic lobar atelectasis" of the lung, and bronchopneumonia an infectious "patchy atelectasis." It is only after these conditions have been induced that consolidation and the other features characteristic of pneumonia, cyanosis, toxemia, and bacteremia are developed.

TREATMENT WITH CARBON DIOXIDE

At this point Haggard and I were privileged to join with Coryllos and Birnbaum in testing such therapeutic value as inhalation of carbon dioxide might have. With the collaboration of our colleagues we carried out two series of experiments: one for the production of simple atelectasis, the other for the production of pneumonia. These may be considered as repetitions and confirmations of their previous work. Then, using the experience that our work on the relief of asphyxia and related conditions had developed, we tested the remedial value of inhalation of carbon dioxide in simple atelectasis and in pneumonia, and compared the results of these two parallel series of experiments. It is this comparison which is particularly significant.

Experiments on Atelectasis. In the first of these two series of experiments twenty-four large dogs, weighing from 12 to 25 kg. were used. They received, by intraperitoneal injection, a sufficient dose of amytal, so that within fifteen minutes they sank into a deep narcosis which lasted for twelve to twenty-four

hours. An X-ray picture of the chest was taken to insure the normality of their lungs. Then by means of a bronchoscope one of the small balloons devised by Coryllos was inserted in the right bronchus and inflated with water, so as to shut off, as nearly as possible, all the branches of the bronchus. Then the animal was laid on its right side on the floor where it remained in profound narcosis for many hours.

Next day, a second X-ray picture was taken. It showed in all cases a complete atelectasis in all the lobes of the right lung corresponding to the branches of the bronchus that had been occluded. The animals were then etherized; and with the bronchoscope the balloon was removed from the bronchus. Immediately thereafter they were placed in a large chamber (12 cubic meters) into which enough carbon dioxide was also introduced, and mixed with an electric fan, to bring the concentration of this gas up to about 6 or 7 per cent. Under these conditions the ether that they had inhaled was quickly eliminated, and the animals moved about in the chamber. They breathed deeply but appeared comfortable and sometimes slept.

After thirty to sixty minutes in the chamber the animals were removed and another set of X-ray pictures was taken. They showed in all cases a practically complete reinflation of the previously atelectatic lungs. This rapid restoration of normality was the more striking because Coryllos and Birnbaum in an earlier series of such experiments had found that, after removal of the balloon, if the dogs were left to recover unaided, the reinflation was not complete for several hours. Clear evidence of the effectiveness of deep breathing and other movements of the chest was also afforded by one experiment in which, after removal of the bronchial plug, the animal was kept under light ether anesthesia and struggling in a state of excite-

ment for half an hour. The previously entirely atelectatic lung was then found to be fully reinflated.

Experiments on Pneumonia. In a second series of experiments twenty-eight dogs were narcotized as before. A virulent culture of pneumococci of type II, concentrated by the centrifuge, was insufflated through a catheter deep into the right bronchus. Two of these animals were found dead next morning, presumably of barbiturate poisoning. Four failed to develop pneumonia. Of those that did develop pneumonia, six were left without further treatment and died a day or two later with a fully developed unilateral pneumonia, as had been the case in nearly all of the earlier experiments of Coryllos and Birnbaum. Of the remaining sixteen dogs in our series all within 24 hours had developed an acute pneumonia.

On the day following their infection, X-ray pictures were taken and showed in all sixteen of these animals an atelectasis as marked as in the previous series. They were then placed in the closed chamber in an atmosphere of air to which 6 or 7 per cent of carbon dioxide was added. They were at that time so ill that several could not lift their heads from the floor. In order to satisfy their extreme thirst, their heads had to be lifted by hand and held over a pan of water. Yet after periods of from 2 to 24 hours in the atmosphere containing carbon dioxide the atelectasis was found to have cleared up and within 24 to 48 hours thirteen of the sixteen animals made complete recoveries. In two of the three which died, autopsy showed a suppurative pneumonitis, probably due to bacillus coli, as occurred also in some of the dogs in the previous series a couple of days after withdrawal of the bronchial plug.

Comparison of Simple Atelectasis and Pneumonic Atelectasis. Full details of both of these series of experiments will be found

in our original paper. But for the sake of comparison of the degree of atelectasis induced merely by a bronchial plug and

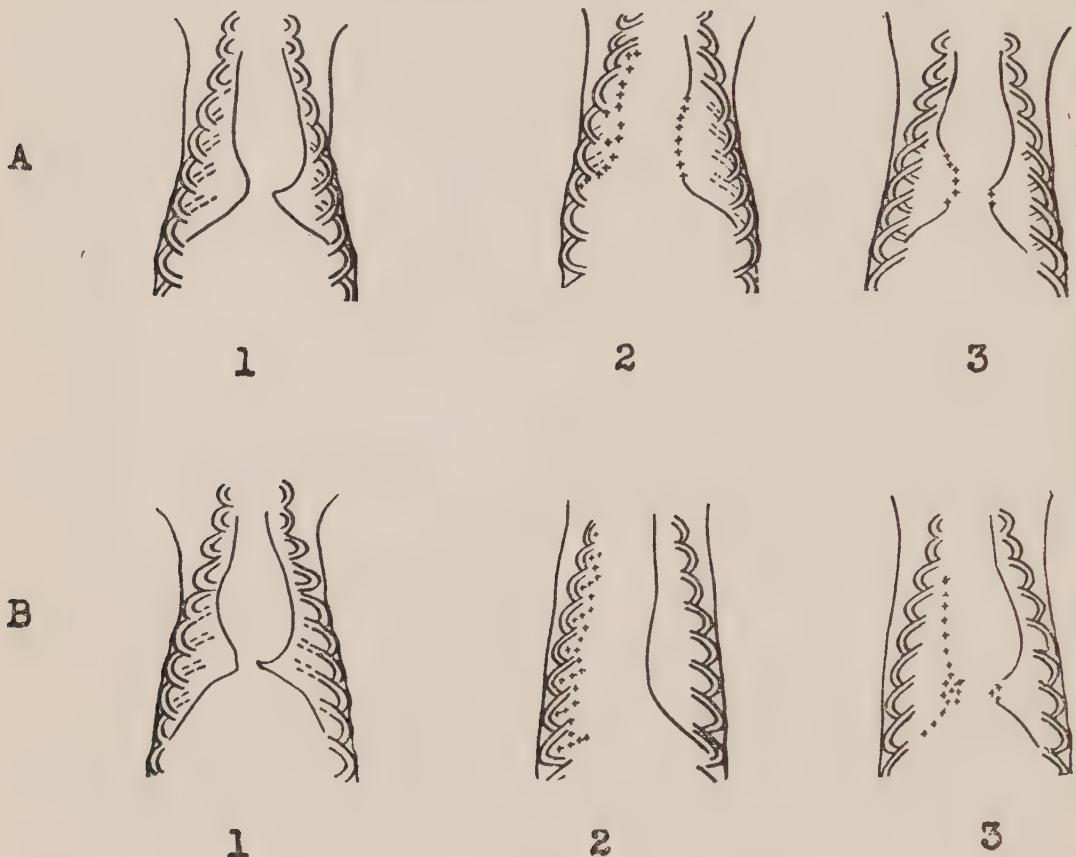


FIG. 8. Outlines of the thorax, drawn from x-ray pictures, showing in dog A (1) the normal condition, (2) atelectasis of the right lung induced by a plug in its bronchus, and (3) the reinflation of the lung under inhalation of carbon dioxide; and in dog B (1) the normal condition, (2) the atelectasis incident to a unilateral pneumonia, and (3) the reinflation of the lung, and cure of the pneumonia, under inhalation of carbon dioxide. For five similar pictures of each type of atelectasis, and a more extended discussion of the production and relief of pneumonic atelectasis, see Arch. Int. Med., 1930, 45, 77 and 85.

that occurring in pneumonia, line drawings were traced from the X-ray pictures of a typical case in each series of experiments. They are reproduced in figure 8. They show the out-

lines of the ribs, diaphragm and heart: (1) normal, (2) in atelectasis and (3) after recovery. The drawings marked (A) show the course of events in simple obstruction. Those marked (B) show the same series for pneumonia.

It is noteworthy, however, that in the first series of experiments—those of simple atelectasis from obstructed airways—less than an hour in an atmosphere containing carbon dioxide was sufficient to induce a complete reinflation of the lung. In the pneumonia experiments, on the contrary, much longer periods—periods from 2 to 24 hours—were required.

It would, I think, be impossible to ask for clearer or more decisive experimental evidence than these figures afford in support of the three propositions:

- (1) That atelectasis is a factor in pneumonia.
- (2) That without atelectasis infection does not develop into pneumonia.
- (3) That early relief of atelectasis, with clearing of the airways and reinflation of the lung, induces a rapid recovery from pneumonia.

CARBON DIOXIDE AS A BACTERICIDE

The success of these experiments in curing pneumonia was so striking as to raise a question as to their full explanation. Were these cures due merely to dilation of the lungs? May there not be some auxilliary factor which is also called into play by carbon dioxide?

Little is known of the reason why, in clinical cases of pneumonia that recover, the pneumococci cease to multiply and die out; or of the chemistry of resolution of the pulmonic exudate. The following facts, as presented by Lord, may however have

an important bearing. The pneumococcus is, he says "very sensitive to change in the reaction of media in which it grows. Its extreme sensitiveness to acid may be better appreciated when it is stated that the range between the slightly alkaline reaction of normal blood and that of the culture containing glucose in which death of the organism takes place is about that between ordinary tap water and distilled water standing in the laboratory.... As the inflammatory process in the lung goes through its evolution . . . the reaction, so far as we can learn from animal experiments and tests of the lung immediately after death, changes from slightly alkaline to a degree of acidity within the range of the acid death point of the pneumococcus.... At an acidity corresponding to that which the inflammatory process may reach, the duration of life of the pneumococcus in fluid culture media without serum is only about two hours.... In explanation of the factors contributing to recovery from a chemical point of view it may be conceived that as the evolution of the local process takes place with an increase of acidity . . . the acid death point of the pneumococcus is reached."

As regards the influence upon resolution of the pulmonic exudate of even a slight acidity Lord further remarks, "Two enzymes are demonstrable in the pneumonic lung, one active in slightly alkaline, neutral, and slightly acid media and another with optimum activity in still more acid media. As the evolution of the pneumonic process takes place there is an increase in cells containing ferment, a diminution of serum containing antifерment, and a shift to an acid reaction.... Increase of cells (enzymes), diminution of serum (anti-enzymes), and a shift to an acid reaction thus permit the melting away of the exudate and restoration to normal."

In addition to the statements thus quoted it may be pointed out that, although carbonic acid is a very weak acid, its acidity in media not too heavily buffered with protein and salts is sufficient to reach the degree (that is the lowering of pH) requisite for at least partial inhibition of the growth of pneumonic exudate. It affords the sole means that present scientific knowledge appears to offer for attack upon the pneumococcus along the lines here indicated. But in order to exert an effective bactericidal and resolving action carbon dioxide inhalation needs the assistance of morphine or some other respiratory depressant drug.

THE CLINICAL USE OF CARBON DIOXIDE

Pneumonia as it occurs clinically is very far from being the uniform disease that can be induced experimentally. It is in fact probably the most variable of all infectious diseases. Modern medicine tests the efficiency of every treatment of disease by means of statistics. And for proof of the efficiency of any treatment of pneumonia it would be necessary to offer the statistics of perhaps a thousand cases of which half had received the treatment in question and half had not.

There is as yet, therefore, no clinical evidence at all comparable to the experimental evidence above set forth. But there is nevertheless a sufficient amount of evidence of a suggestive character to justify the hope that before long in some large hospital the value of the inhalational treatment of pneumonia will be subjected to a full statistical test.

Very suggestive however are the large number of reports—amounting altogether to some thousands—that have come to me of the use on pneumonia patients of the inhalator which Haggard and I have introduced for the resuscitation of the

victims of carbon monoxide asphyxia. Many physicians in many cities have found and reported to me by letter that the administration of the mixture of oxygen and carbon dioxide which these inhalators contain not only overcomes cyanosis, but is also an effective stimulant in acute pneumonic depression. The benefit is doubtless in part due to the deeper breathing under this inhalation; for Meakins has shown that the shallow breathing in pneumonia is a potent factor in the production of anoxemia. In part also the benefit is due to support for the circulation through the influence of carbon dioxide upon the venous return.

In pneumonia two modes of death may be distinguished, although both are usually involved. In one the decrease in the oxygen content of the arterial blood induces an asphyxia essentially like that under carbon monoxide. In the other toxemia depresses muscle tonus, and thereby decreases the venous return to such a degree that the circulation fails. For the first the obvious counteractor is oxygen; for the second, carbon dioxide.

The largest groups of cases treated with the inhalator have each numbered several hundred and have generally been among the employees of city electric lighting companies in which the management maintains an efficient medical department, notably that of the Brooklyn Edison Company under the direction of Dr. J. J. Wittmer. The observations of Dr. J. T. Alison on bronchopneumonia in children also indicate distinct benefit from inhalation of carbon dioxide with oxygen. In many hospitals it has been found that in the oxygen tents used to relieve cyanosis the accumulation of one or two per cent of carbon dioxide induces no objection from the patients, as higher percentages do, and is apparently beneficial.

The most direct use of inhalation of carbon dioxide in the early treatment of pneumonia has been made by Drs. Gunther and Blond in Los Angeles. As they have employed it, pure carbon dioxide is administered by means of an open mask in which the gas, supplied at the rate of 2 or 3 liters per minute, mixes with the inhaled air. With a volume of breathing increased thereby to 20 or 30 liters per minute this amount of gas produces from 5 to 7 per cent in the inhaled air. The inhalation is given for only a few minutes at a time, but long enough and strong enough to induce marked hyperpnea. After five minutes rest the inhalation is repeated; and thereafter these two inhalations are administered at regular intervals of three or four hours. "The first inhalation generally causes severe coughing, which brings up a surprisingly large amount of yellow pus. The patient is considerably fatigued, but drops asleep and awakens feeling and appearing better. Resolution occurs earlier than in untreated cases."

The series consisted of 195 cases in the city of Los Angeles during the years from 1931 to 1935 inclusive. Of these 112—75 broncho-pneumonia, and 37 lobar pneumonia—received no inhalational treatment. The deaths from broncho-pneumonia were 10, from lobar pneumonia 9; total 19, or 17 per cent. Oxygen or oxygen and small amounts of carbon dioxide, insufficient to induce coughing, were administered to 37 cases—29 of broncho-pneumonia and 8 of lobar pneumonia—of whom 5 in the first group and 1 in the second died; total 6, or 16 per cent.

With these cases as controls are to be compared the cases, 46 in number, that were treated with inhalation of carbon dioxide as described—33 broncho-pneumonia and 13 lobar pneumonia. Of these only one in each group died: total 2, or 4.3 per cent. It is noteworthy also that, in the untreated cases

that recovered, fever lasted for an average of 11.5 days in those with broncho-pneumonia, and for 13.7 days in those with lobar pneumonia. In the treated cases the fever in the patients with broncho-pneumonia lasted for an average of only 4.3 days and in those with lobar pneumonia for an average of only 5.2 days.

Recently Gunther has noted in some patients who were seen immediately after the sudden onset of their illness, a condition that exactly corresponds to the pure atelectatic stage, which according to Coryllos may precede true pneumonia. In these cases the illness began abruptly with severe prostration, high fever and marked cyanosis. To all appearance they were suffering from pneumonia. The physical signs were dullness to flatness, and suppression of the breath sounds with or without suppression of vocal sounds at one base. These patients were clinically well within 24 hours after carbon dioxide inhalations were begun.

In medical science and particularly in therapeutics there are two distinct methods of establishing facts: experiments and statistics. This chapter reports experiments. But in such a disease as pneumonia any treatment must be evaluated finally on a basis of statistics. And as regards inhalational treatment sufficient statistics to be decisive are still lacking. But they should not be lacking long.

Chapter XIV

FAILURE OF THE CIRCULATION

THE large majority of all deaths occur through failure of the circulation. With the cessation of the flow of blood, the supply of oxygen to the tissues ceases. Failure of the circulation becomes a form of asphyxia. But its most easily measured feature is the progressive fall of arterial pressure. Along with other features of depression of vitality, low arterial pressure is induced by a wide variety of accidents, injuries and diseases. It often ends in death. How then does the circulation fail?

Up to the end of the nineteenth century few instruments had been introduced to measure and record the phenomena of the living human body. For diagnosis physicians had to rely mainly on their unaided senses. In regard to the pressure and flow of the blood they had no better aid to knowledge than the "tactus eruditus of the trained finger" on the radial artery, plus the sound of the heart. Judged by such elementary means the heart of a dying man appears to beat more and more feebly. At last it seems to stop. Actually it often fibrillates for a few minutes before the final standstill and complete relaxation. On the basis of such evidence as they had, the early observers could draw only one conclusion regarding failure of the circulation. They said: It is the heart that fails.

THE CONTROL OF ARTERIAL PRESSURE

In 1628 William Harvey demonstrated that the function of the heart is to pump the blood into the arteries. Through the

arteries the blood flows to all parts of the body and then back to the heart through the veins.

Two hundred years ago (1733) Stephen Hales demonstrated and measured the pressure of the blood in the arteries. He attached a vertical glass tube to one of the arteries of a horse; and when the artery was opened, he saw the blood rise in the tube for a distance of 8 feet, 3 inches. At that height the column pulsated through a range of several inches.

A hundred and ten years ago (1828) Poisseuille first used a mercury manometer, instead of a column of blood, to measure the pressure in the artery of an animal. And in 1847 Karl Ludwig placed a float on top of the column of mercury, and arranged for the float to record the pressure on a smoked drum. In the graphic records of arterial pressure each beat is shown as a wave, and usually each respiration also. Stimulation of a sensory nerve causes the curve to rise. Stimulation of the vagus nerve causes the heart to beat more slowly, or even to stop for a few seconds; and with this slowing or standstill of the heart, arterial pressure falls. Cutting the splanchnic nerve induces a lowering of the curve; stimulation of this nerve induces a rise. A small loss of blood has no appreciable effect on the height of the curve; but extensive hemorrhage lowers it until, with the final failure of the circulation at death, it drops to the base line; and arterial pressure falls to zero. These and similar experimental facts are the basis, laid largely by Ludwig and his pupils two or more generations ago, upon which is built the physiology of arterial pressure and its control by the vasomotor nervous system.

A CELEBRATED EXPERIMENT

One of the most celebrated of all experiments on the circulation, but also one that has been long and widely disputed, is the

so-called "Klopfversuch" first described by Goltz in 1865, and referred to in chapter II. It is performed on a vigorous, and generally squirming, frog. The animal is held by the legs while its abdomen is slapped smartly. As the result of this insult, all the muscles of the body relax; breathing may stop for a time; and the cutaneous reflexes are temporarily abolished. The heart slows, or even stops momentarily. When the heart beats again, it is seen to be nearly bloodless; and this condition is accounted for by the fact that the abdominal viscera are congested with blood. Evidently there has been a general relaxation of the vessels of the splanchnic area, both the arteries and veins. Evidently also this relaxation is not merely the direct effect of the insult to the viscera, but is induced through a reflex by way of the spinal cord. The entire series of events in the frog is essentially the same as that which occurs in a prize fighter, who is knocked out by a blow over the solar plexus.

Early in the present century the sphygmomanometer was introduced for the measurement of arterial pressure in patients. With this instrument it was found that, alike after acute illness, serious physical injuries and major surgical operations, arterial pressure may fall to a low level, and that this fall occurs long before the heart ceases to beat. Thus in men, as already in animals, attention was diverted from the heart to other factors in the circulation; and it was recognized that it may be the failure of one of these other factors that accounts for the low arterial pressure in a failing circulation.

But, however it is caused, it is unfortunate and illogical that this state of low arterial pressure, which is really only one feature of the depression of the vitality of the entire body, should ever have acquired its modern name: "shock." The term "hypotonia" would fit all theories. In ordinary use the word shock signifies a jolt or concussion. In physiology and surgery it is

now taken to signify a rather long continued state of relaxation of the arteries. And actually, as will here be shown, it is not that either.

SHOCK AS HYPOTONIA FROM CONCUSSION

Modern surgery was the product of the nineteenth century. With the elimination of pain by anesthesia and infection by asepsis, a vast range of new problems could be attacked. Among the most imperative of these problems was—and to some extent still is—that of the profound depression of vitality that often follows severe accidental injuries and that sometimes occurs also after major surgical operations. It is a state like that induced by extensive hemorrhage, although it may develop without loss of blood. Nothing that can be found at autopsy explains this depression. It is in fact still largely unexplained. Yet even in the later years of the eighteenth century, 150 years ago, John Hunter had recognized and described it. He conceived it as due to a subtle vibration that temporarily paralyzes the tissues and organs of a part or all of the body.

In 1793, in discussing "union by the first intention," Hunter wrote: "That injury which in its nature is the most simple, and yet calls forth the actions of the part to recover from it, is a degree of concussion, where the only effect produced is a debility of the actions or functions of the whole or part, similar to that occasioned by a bruise, in which the continuity of the substance is not interrupted: in such a state the parts have little to do but to expand and reinstate themselves in their natural position, actions, and feelings; and this is what happens in concussion of the brain." And in a footnote he added: "Here I mean concussion as a general term, not confining it to the brain." Astley Cooper later had the same conception; and later still Mansell-Moullin also.

To the condition thus defined, James Latta in 1795 is generally supposed to have been the first to apply the term "shock." But, as I do not find it in his book, I suspect that it originated in Germany as a synonym for "Erschütterung," or concussion.

In 1885 Groeningen published a monograph "Ueber den Shock" which contained 255 large pages and quoted 395 references to the literature of this subject up to that time, beside his own observations. Such a monograph today would have to quote many times more references; and the number is still increasing. Yet the greater part of all this vast mass of writing can be divided under two or three main conceptions.

According to one of these conceptions, as formulated by Brunton, the vasomotor nervous system is depressed; and the resulting low arterial pressure and insufficient supply of blood induce all of the other depressions of functions. According to a broader conception, it is the centers of the central nervous system—particularly those of the medulla and the spinal cord—that are depressed; and the low arterial pressure is merely one of the manifestations of the resulting general depression and hypotonia of all the organs and functions of the body. According to another conception, sometimes combined with the first, the capillaries become pervious to the blood serum and the volume of the blood is thereby decreased. But, as this condition develops late it is probably due to asphyxia of the tissues after the circulation has begun to fail; for, as Barcroft has pointed out, asphyxia can result from failure of the circulation as well as that from failure of respiration.

The first of these general conceptions was most clearly formulated in a classic paper by Hermann Fischer in 1870. Basing his explanations upon the "Klopfversuch" of Goltz and upon his own wide observations of patients after severe physical injuries and surgical operations, he concluded that failure of the

heart itself can be eliminated from consideration. As Fischer expressed it: "Goltz by his brilliant experiment has shown . . . that when the heart begins to beat again (after the standstill) it exhibits a striking deficiency of blood. The circulation therefore is small or lacking in spite of the heart's activity. . . . And this ineffectiveness of the heart is due to a temporary paralysis of the tonus of the blood vessels throughout the entire body, but particularly those of the abdominal viscera." Fischer therefore defined shock as a "reflex paralysis of the vasomotor nervous system" induced by a traumatic "Erschütterung"; and this German word means vibration, shaking, concussion, or, in its ordinary mechanical sense, shock.

This conception was adopted by Crile in this country in 1899 and by a long list of others. It is still widely prevalent. It has also been refuted by a number of investigators: among others by Groeningen, Porter and myself. The main reasons that it still persists appear to be two in number: One is that arterial pressure has generally been the only function recorded in the investigations on this subject. If body temperature, or metabolism, or respiration, or consciousness, or nearly any other function had been observed with equal care, each and every one of these functions would have been found to be quite as definitely depressed as arterial pressure. The second reason is that physiologists have generally figured the mechanics of the circulation almost entirely in terms of the heart and the vasomotor nervous system. Beside these two they have recognized no other major mechanical factor. Elimination of heart failure has therefore left no alternative, but failure of the vasomotor nervous system, to explain a state of low arterial pressure.

HYPOTONIA IN THE INFECTIOUS DISEASES

Accordingly, when the problem of the failure of the circulation during and after acute disease was studied, the same conclu-

sion was reached as that in regard to surgical shock. In pneumonia, diphtheria, typhoid fever and many other diseases, depression of the circulation occurs, and often leads to death. In 1899 Romberg and Pässler published an extensive experimental investigation of toxemic shock or hypotonia; and their conception was almost universally accepted. T. C. Janeway wrote in 1907 that the conclusions of Romberg and Pässler "have never been controverted. . . . They clearly demand that we shall in most cases abandon the idea of cardiac death at the height of acute infectious diseases, such as pneumonia, typhoid fever, diphtheria, and the septic fevers; though sudden death during convalescence may be due, at least in part, to the later development of lesions in the heart muscle. In place of heart failure, we must write vasomotor failure, or collapse; the heart stopping only because so little blood is returned to it."

Assuming that failure of the circulation must be due to failure of the vasomotor nervous system, many investigators have attempted to determine and define the nature of that failure. What is the condition in the cells and fibers of the sympathetic nervous system, of which the vasomotor is a part, during its supposed failure? Is it fatigue, or inhibition, or paralysis, or some other form of depression: empty distinctions involving no real difference. And throughout this long discussion, it has been assumed that the vasomotor nervous system must control not only the pressure of the blood in the arteries, as it does; but also the pressure and volume of the blood flowing back to the heart through the veins. There lies the error.

FAILURE OF THE VENOUS RETURN

On one point unanimity and certainty have finally been reached: Alike in traumatic, surgical and toxæmic depression the circulation fails because of the deficient volume of blood that returns to the heart through the veins. In a patient in shock,

or hypotonia, the veins are empty and collapsed, as is plainly to be seen in the jugulars. And recognition of this fact is of the utmost importance; for it decisively contradicts the idea, long and widely held, that "in shock a large portion (of the blood) accumulates in the venous trunks, a state equivalent to an intravenous hemorrhage." So wrote Crile in 1906; and, although he later adopted a broader view, some writers still assume that in hypotonia or shock there must be an "acute venous congestion." Yet, if this were true, the heart would be well supplied with blood and would pump a full volume into the arteries. As the heart is still sound and capable, it fails and arterial pressure falls for lack of a supply of blood flowing from the tissues into the veins, and through the veins back to the heart.

Hypotonic failure of the circulation is almost the exact opposite of the failure of the circulation that is produced by acute valvular disease of the heart. In that condition an intense venous congestion develops because the venous return, although perhaps no more than normal, is yet more than a damaged heart is capable of pumping onward into the arteries.

The question, how the circulation fails in hypotonia, requires first the solution of the problem, how is the venous return normally controlled and regulated? What is the nature of the veno-pressor mechanism? Venous pressure is not easy to measure with certainty; it is the resultant of too many factors. What is needed is rather the measurement of the volume of the blood that is flowing through the veins to the heart.

On this point the volume curve of the heart is the best indicator. In an animal that is going into shock, long before any other symptoms develop, the volume curve shows a slowed diastolic filling and a diminished stroke volume. At this stage arterial pressure does not fail. Even when the output of the

heart has been considerably diminished, the only effect notable in the arterial system is a pulse that is increasingly small and "thready." Evidently the nervous control of the arteries, instead of failing, is brought into increased activity in the effort to maintain arterial pressure and compensate for the diminished output of the heart. This vasoconstriction is exactly like that which Wiggers found in hemorrhage as the explanation of why a considerable volume of blood can be withdrawn from the body before arterial pressure is appreciably lowered. Yet this compensatory and protective reaction has even been regarded by some investigators as itself the cause of shock.

During this period the arterial blood contains a normal amount of oxygen. But, as the amount of oxygen consumed in the tissues is not yet greatly decreased, the oxygen in the venous blood diminishes in proportion as the volume of the circulation diminishes. When the content of oxygen in that blood has fallen nearly to zero, and the diminished flow of blood no longer supplies the needs of the tissues for oxygen, then catastrophe develops rapidly. The tissues are asphyxiated. The venous return and the output of the heart become so small that the most extreme contraction of the terminal arteries fails longer to maintain arterial pressure. Under the influence of asphyxia the walls of the capillaries become permeable, and the blood undergoes an absolute decrease. Finally the permeability becomes so extreme that saline can be poured into the blood vessels until all the tissues of the body are waterlogged, without restoring arterial pressure. Death by asphyxia soon follows.

THE VASOMOTOR NERVOUS SYSTEM AND THE VENOUS RETURN

Many investigators (Mall, Bayliss and Starling, Burton-Opitz, Plumier, Stolnikow, Roy and Brown, Carl Tigerstedt,

Hooker, Golwitzer-Meier, Rein, Blalock, Freeman and others) have demonstrated that an increase of vasomotor activity may induce a rise of venous pressure and an increase of the venous return to the heart. But the effects on both the pressure and volume in the veins are only momentary, while the effect on arterial pressure may be almost indefinitely prolonged. On this point S. C. Harvey and I obtained decisive evidence. We injected adrenalin into the veins of decapitated cats and saw both arterial and venous pressure rise. But when the injection of a moderate amount of the drug properly diluted was injected continuously for a period of several minutes, although arterial pressure was raised to a high level and was there maintained, the pressure in the jugular vein, on the contrary, after a momentary rise, returned virtually to its original level and there remained. A typical experiment was as follows:

Experiment showing that arterial pressure can be maintained at a high level by a continuous injection of adrenalin, but that venous pressure can not

Cat, decapitated. Insufflation. Slow injection of adrenalin, during 4.5 minutes.

	ARTERIAL PRESSURE	VENOUS PRESSURE
	mm. mercury	mm. saline
Before injection	40	0
30 seconds after starting injection	150	20
1 minute	150	20
2 minutes	140	10
3 minutes	130	5
4 minutes	120	5
4.5 minutes, injection stopped	—	—
5 minutes	100	0

Result: Although venous pressure rose at first it fell again even during the injection nearly to its initial level.

Other experiments of the same general type—the type that Karl Ludwig would have used, if he had attacked this problem—yielded confirmatory results. In a morphinized and curarized dog under artificial respiration the spinal cord was cut just below the occiput. Arterial pressure fell greatly, but venous pressure fell only slightly, or sometimes even rose slightly. The sciatic nerve was then stimulated electrically. Arterial pressure rose considerably, but venous pressure only minimally. A typical experiment was as follows:

Experiment showing that a strong vasomotor reflex may have a scarcely perceptible effect on venous pressure

Dog; 9 kilos. Venous pressure from jugular. Insufflation. Animal curarized. Spinal cord cut. Left sciatic nerve exposed and cut. Central end of nerve stimulated electrically.

	ARTERIAL PRESSURE	VENOUS PRESSURE
	mm. mercury	mm. saline
Before stimulation	70	25
Stimulation of sciatic for 6 minutes:		
1st minute	80	30
2nd minute	90	30
3rd minute	100	30
4th minute	110	30
5th minute	120	30
6th minute	130	30

Result: After section of the spinal cord stimulation of the central end of the sciatic nerve caused arterial pressure to rise gradually from 70 to 130 mm. without a corresponding effect on venous pressure.

CARBON DIOXIDE AND THE VENOUS RETURN

It is largely through the production of carbon dioxide that respiration is correlated with muscular activity. It would be logical—or at least purposeful—if carbon dioxide exerted a similar correlating influence upon the volume of the circulation.

As the volume of the venous return is one of the two main factors in the volume of the circulation—the other being the heart rate—it seemed probable that carbon dioxide might play an important part in the venopressor mechanism.

Experiment showing that carbon dioxide has a far greater effect upon venous pressure than upon arterial pressure

Cat, beheaded. Insufflation with oxygen, then oxygen plus 15 per cent of CO₂, and finally oxygen alone.

	TIME minutes	ARTERIAL PRESSURE	VENOUS PRESSURE
		mm. mercury	mm. saline
Oxygen alone	0	50	0
Oxygen + CO ₂	1	50	0
Oxygen + CO ₂	7	52	10
Oxygen + CO ₂	16	58	30
Oxygen + CO ₂	19	58	40
Oxygen + CO ₂	20	60	45
Oxygen alone	22	60	60
Oxygen alone	23	60	50
Oxygen alone	24	60	45
Oxygen alone	25	60	35
Oxygen alone	26	60	25
Oxygen alone	27	55	10
Oxygen alone	28	55	0

Result: Under CO₂ venous pressure rose during 22 minutes from 0 to 60 mm. while arterial pressure rose only from 50 to 60. The amplitude of the pulsations in the arterial pressure record was markedly increased. Later during 6 minutes under oxygen alone venous pressure fell to its original level and arterial pressure sank slightly.

That carbon dioxide does in fact play such a part is evidenced by the distended veins that have long been a recognized feature of suffocation of the Desdemona type. Deficiency of oxygen is not the cause of the venous congestion. For during the Great War hundreds of candidates for the Aviation Service were tested

on rebreathing apparatus, with absorption of carbon dioxide, but progressive decrease of oxygen, until they fainted. No venous congestion appeared. On the contrary in tests of apparatus for mine rescue, in which ample oxygen was supplied, enormous congestion of all superficial veins always developed, whenever there was an accumulation of carbon dioxide.

Experiments that S. C. Harvey and I performed on decapitated cats demonstrated this relation. The animals were maintained by intratracheal insufflation of oxygen, to which for short periods 15 per cent of carbon dioxide was added. A typical experiment is shown on page 238.

These experiments contrast sharply with those in the preceding section. They demonstrate that the vasomotor nervous system exerts a strong direct influence on arterial pressure, but relatively little on the venous return. Carbon dioxide, on the contrary, exerts relatively little direct influence upon arterial pressure, but a powerful influence upon the venous return. If, as all authorities now concede, hypotonic failure of the circulation is due to failure of the venous return, the failure is not in the vasomotor nervous system.

Chapter XV

THE VENOUS RETURN AND ITS FAILURE

"**T**HE venopressor mechanism consists in part of the tonus of the tissues. This tonus prevents stasis by compressing the capillaries. When it is diminished the blood stagnates in the venous reservoirs, that is, in the capillaries. The respiratory center exerts an indirect but powerful control over the venopressor mechanism." So I wrote in 1910.

In that year Coffey, Barnum and I looked for an experiment to test whether conditions that influence the respiratory center may not also influence the tonus of the entire skeletal musculature of the body. As an index of tonus we used the knee jerk. Uniform strokes of a small hammer were applied to the patella tendon; and the extent of the reactions was recorded graphically under three conditions: (1) natural breathing, (2) during apnea vera after forced breathing, and (3) while the subject was in hyperpnea from rebreathing the air in a bag. The record here reproduced shows that the knee jerk was practically abolished during apnea, but was exaggerated during hyperpnea. From this and other evidence it appears that the tonus of every muscle in the body is influenced sympathetically by the degree of excitement and activity of the respiratory center, as King, Blair and Garrey also find. Additional observations showed that respiration has so marked an influence that in a normal man muscle tonus rises with inspiration and falls with expiration.

There the matter rested until in 1929 Riml published a striking experiment. In this experiment, which we have repeated and verified, the thorax of a cat in deep narcosis is opened. The

pulmonary artery is clamped, thereby bringing the circulation to a sudden and complete standstill. Immediately a trochar is thrust into the right heart; and the pressure and volume of the outflowing blood are determined. The result is extraordinary. A half, or more, of all the blood in the body gushes

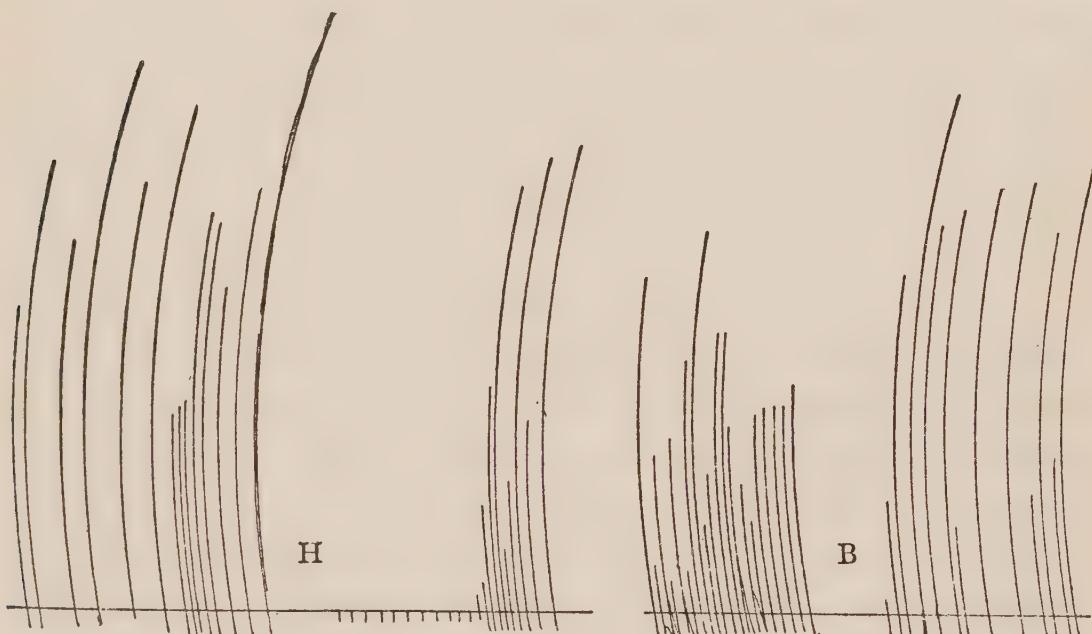


FIG. 9. Knee jerks, indicating degree of tonus, elicited by uniform mechanical stimuli at intervals of 3 seconds. The first 14 kicks were recorded under normal conditions. The stimuli were then stopped (at *H*) while the man performed forced breathing for 45 seconds. An apnea of 18 seconds followed, during and after which 11 stimuli (indicated by short strokes below the baseline) elicited no response. Then the reflex returned. After 15 minutes rest the experiment was repeated, except that during the forced breathing (at *B*) a small paper bag was held over the nose and mouth. No apnea followed, and the kicks were accentuated. (From Am. J. Physiol., 1910, 25, 320.)

out under a pressure sufficient to support a column of blood 10 or 12 cm. in height.

Where does this blood come from; and what is the force that drives it through the veins toward the heart? Obviously it comes from the reservoirs of blood in the tissues. Obviously

also the heart is not involved; for its force is abolished by the clamp on the pulmonary artery. The pressure is produced within the tissues, and is due to their tonus; for it disappears along with their tonus a few minutes after death. Muscle tonus is therefore the force that produces this pressure and with it the flow of the blood through the veins to the heart. Riml's experiment reveals at least one of the factors in the venopressor mechanism.

The vasomotor nervous system is not involved; for the experiment worked well on a sympathectomized cat that Professor Cannon kindly gave me. It had no vasomotor nervous system.

TONUS AND INTRAMUSCULAR PRESSURE

That each muscle as it contracts squeezes some of the blood from its capillaries into the veins and on toward the heart is an idea as old as William Harvey and Borelli. It is also well recognized that the intra-abdominal pressure—the pressure upon the viscera due to the tonus of the diaphragm and the muscles of the body walls—affords support to the venous return. Emerson measured this pressure; it is small, but important. No one seems, however, to have suggested that there is a pressure within the tissues, particularly the muscles, induced by their constant tonic pull, essentially as a pressure is induced between the strands of a rope under tension.

To complete the evidence it was essential to determine whether or not in the muscles of normal men there is this pressure; its amount, its variations and particularly its decrease with physical weakness and loss of tonus. In order to make such determinations the apparatus shown in figure 10 was devised and used in the manner described in the legend. The results which Oughterson, Greenberg, Searle and I obtained, and which have been confirmed and extended by Kerr and Scott in Glasgow,

and by Beiglböck and Junk in Professor Eppinger's clinic in Vienna, were as follows:

In healthy young men the pressure in the relaxed, but tonic

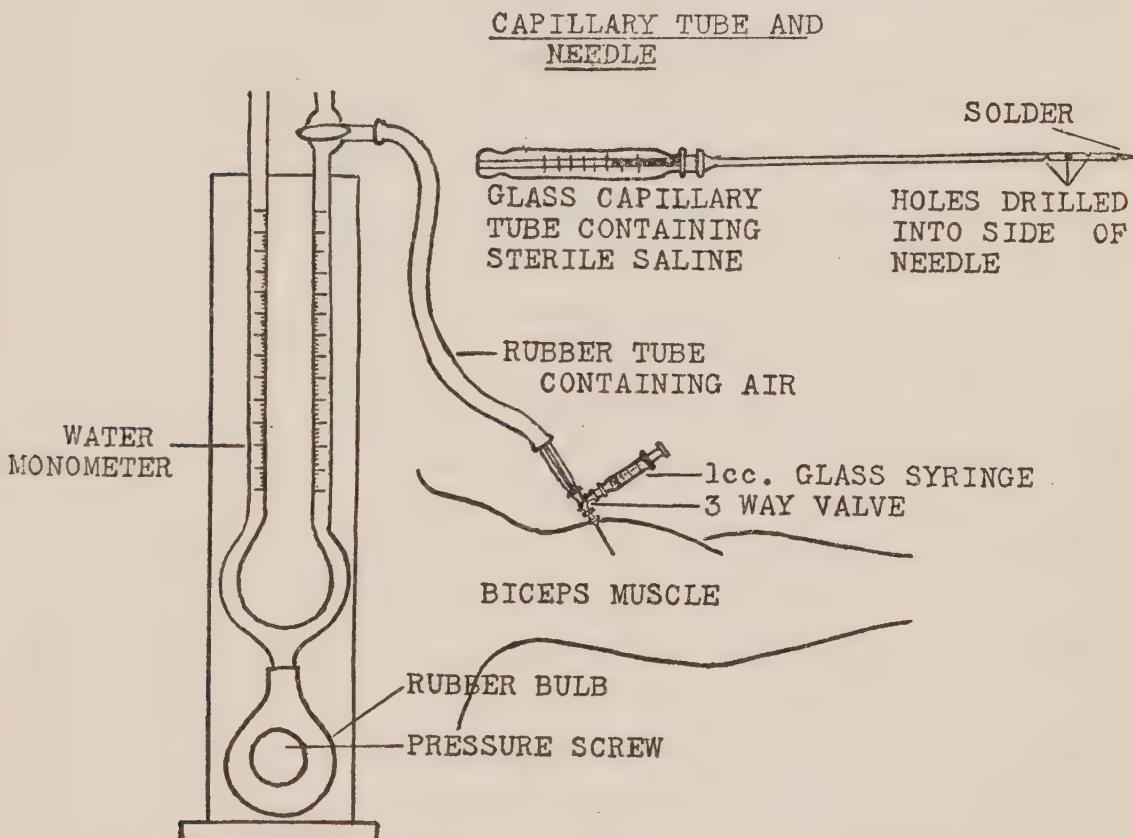


FIG. 10. Showing the apparatus (as modified by Kerr and Scott) used to measure intramuscular pressure. A hypodermic needle (No. 20 American, or 4 British) is used. The end is closed with solder and three holes are drilled in the sides near the end. The needle is connected by means of a 3 way valve to a small syringe and a piece of capillary glass tube, 5 cm. in length and 1 or 2 mm. bore; and this in turn by a rubber tube containing air connected to a U-tube manometer graduated in millimeters in which a column of water can be raised by a thumbscrew on a rubber bulb.

The subject lies on his back. An area of skin over the left biceps is sterilized and anesthetized. With the elbow flexed to about 135 degrees, the needle is inserted into the middle of the muscle. Enough sterile saline solution is introduced from the syringe into the capillary to make a meniscus visible. One observer then raises the pressure in the manometer while a second watches the meniscus until it begins to move. He then signals the first observer, who reads the pressure in the manometer. It is the first movement of the meniscus, indicating that the intramuscular pressure has been overcome, that is taken as indicating the tonus and internal pressure of the muscle. The first reading is discarded and the average is taken of the next three.

biceps is from 60 to 90 mm. of water. In patients several hours after major surgical operations the pressure is from 30 to 60 mm. In moribund animals it decreases progressively to zero at death. Strychnine raises the pressure markedly, which explains the support that this drug was formerly believed to afford to the heart. Actually the support is afforded by the increased venous return to the heart. Inhalation of carbon dioxide has a similar effect, while overbreathing, which decreases the carbon dioxide in the blood and depresses the respiratory and spinal centers, has the opposite effect. Stimulation of the skin by air that is moving and feels "fresh" increases muscle tonus and the intramuscular pressure, while "close" still air may decrease them to the point of nausea, or even of fainting from failure of the venous return.

These observations, combined with those in chapter XIV, afford a basis for the conception that the volume of the circulation and the efficiency of the heart are largely determined by the tonus of the musculature of the body. The higher the tonus of the muscles the greater the amount of the energy of the arterial pressure that is conserved in the blood in the capillaries, and that can then be expended in sending the blood from the tissues on through the veins back to the heart. Furthermore, the higher the tonus of the respiratory muscles the greater the expansion of the lungs, and the greater the negative pressure in the thorax. And the "effective venous" pressure, which motivates the filling of the heart, is the total difference between the negative pressure in the thorax and the positive pressure in the tissues and organs of the body (Henderson and Barringer).

In the light of these facts the nature of the influence that hypotonia exerts upon the circulation becomes clear. Failure

of the circulation in traumatic and surgical shock and in the hypotonia of illness is largely due to diminution of general body tonus. As a result intramuscular pressure is lowered and the blood stagnates in the flaccid tissues. Doubtless the capillaries, by the continual alternation of contraction and relaxation, demonstrated by Krogh, also play a part. It is well known that carbon dioxide may dilate capillaries. But, if the capillaries alone were the prime factor in the venopressor mechanism, the pressure demonstrated in Riml's experiment would not disappear coincidentally with the disappearance of general body tonus. Muscles and blood vessels withstand asphyxia quite well for fairly long periods; but the central nervous system fails within ten minutes. And it is from the central nervous system that come the impulses that induce tonus in the skeletal muscles. When these impulses over the motor nerves cease, the tonus of the muscles fails. The pressure upon the blood in their capillaries is abolished. The venous return stops. And the circulation fails.

THE MOTOR CENTERS, NOT THE VASOMOTOR, FAIL

In the opening paragraph of chapter XII it was pointed out that of all features of illness the commonest is muscular weakness. In chapter XIV ample evidence has been presented to show that hypotonic failure of the circulation is due to failure of the venous return, and not to failure of the vasomotor control of the arterial system. In support of this thesis four additional pieces of evidence will now be presented.

Curare is a drug prepared from the arrow poison of South American Indians. It was introduced into physiology by Claude Bernard in 1857. Although it has no therapeutic value, it is

an extremely useful means of investigation. It blocks the passage of nerve impulses from motor nerves to muscles; but it has no effect upon the passage of the impulses over vasomotor nerves to the minute nonstriated muscle fibers that surround the arteries and determine their calibre. In an animal moderately drugged with curare stimulation of an afferent nerve therefore induces quite normal vasomotor responses, as shown by a rise of arterial pressure; but no motor responses in movements of the limbs. Yet under an excess of curare the circulation fails; and, as Durdafi observed, the failure is of the hypotonic, or shock, type. It is fair to infer that the excess acts—not by paralyzing the vasomotor nerves—but rather by cutting off the impulses over motor nerves that normally induce muscle tonus. Consequently the blood stagnates in the tissues; and the venous return fails.

Another piece of evidence that appears almost crucial against the Goltz-Fischer-Crile vasomotor conception of hypotonia and shock has in recent years been reported by W. B. Cannon. He has repeatedly removed the entire sympathetic nervous system from dogs and cats. And he reports "that sympathectomized animals continue to live without apparent difficulty" in good health for as long as may be desired. Although Cannon performed this experiment for purposes entirely different from the topic of failure of the circulation and has never suggested this application, his findings certainly demonstrate that the vasomotor nervous system is not essential to the maintenance of the venous return. If failure of the vasomotor nervous system were the condition underlying hypotonic failure of the circulation, sympathectomized dogs and cats should survive only in a state of chronic shock. Actually, as Bradford Cannon finds, they are quite healthy.

SPINAL ANESTHESIA AND FAILURE OF THE CIRCULATION

A third piece of evidence as to the nature of hypotonic failure of the circulation is afforded by the experience of many surgical clinics in the use of spinal anesthesia. The anesthetic is introduced into the spinal canal with the intention, and generally also the result, that only the sensory roots of the spinal cord shall be completely blocked. Experience demonstrates, however, that the drug may also reach the motor roots and paralyze them as well. In such cases there results a condition of the circulation which is in all respects identical with typical surgical shock.

This effect of spinal anesthesia occasionally costs a life. But neither in such fatalities, nor in the cases that recover, is the reason for the depression of the circulation understood. Fortunately the subject has recently been very thoroughly investigated on both the clinical and experimental sides by O. O. Schuberth. As he says: "One of the reasons for spinal anesthesia being regarded with doubt by many is that now and again, there occurs, in immediate connection with the induced anesthesia, a certain shock-like condition indicating a disturbance of the circulation: a decrease in blood pressure, often very considerable; bradycardia, pallor, cold sweat, indisposition and vomiting; the decrease in the blood pressure, being the most prominent symptom and the one most generally discussed. As anesthesia recedes, the symptoms generally diminish."

By extensive citations from the literature of recent years Schuberth shows how far short of finality the conception of shock has as yet developed. It is defined by Phemister and Livingstone as "a state of acutely and severely reduced metabolism brought about through the nervous system by depression of the circulation and to a lesser extent of respiration, from a

severe bodily or psychic shock." Rein, speaking to the German Surgical Congress, defines shock as "a condition of depression of the circulation after severe trauma and certain major operations." It resembles toxemic collapse. Eppinger, one of the most thorough students of the subject, regards surgical shock and toxemic collapse as essentially alike in that both involve, as their principal feature, a "paralysis of the peripheral blood vessels"; and in this general view Gollwitzer-Meier, Mautner and Pick, and Kroetz concur.

On the whole from a survey of the literature Schuberth concludes that the best founded definition is that "shock or collapse is essentially a peripheral circulatory insufficiency."

With this definition as a standard, Schuberth proceeds to show, both by clinical observations and by experiments on animals, that in all essential features the condition occurring in severe cases of hypotonia induced by spinal anesthesia is identical with shock. He points out that when the anesthetic is injected intravenously, no such depression of the circulation is induced. Therefore the effect of intra-spinal injection must be exerted on the roots of the nerves. It cannot be that those fibers in these roots which pass to the sympathetic ganglia are particularly affected; for section of the splanchnic nerves still induces the usual fall of arterial pressure.

Schuberth therefore feels obliged to choose between two ideas: (1) paresis of the vasoconstrictors, and (2) primary respiratory depression (as also often occurs under spinal anesthesia) with secondary circulatory derangement. But neither of these alternatives proves on examination to be entirely satisfactory.

The particular features in which the hypotonia of spinal anesthesia corresponds with those of shock, as Schuberth shows, are: (1) a marked decrease of oxygen consumption; (2) a decreased

output of the heart; (3) a slight decrease in the oxygen content of the arterial blood but a much greater decrease in that of the venous blood, and a consequent large increase of the arterio-venous difference; and (4) in some cases a slight fall of venous pressure. (The pressure was measured in the right auricle and owing to loss of tonus in the respiratory muscles, under spinal anesthesia, as cited in chapter XII, the negative pressure of the thorax was probably decreased.)

Schuberth concludes that: "The decreased cardiac output depends, not upon heart failure, but upon an impaired venous return to the heart. The cause of the circulatory disturbance lies in the periphery." And that in the hypotonia of spinal anesthesia there is "a peripheral circulatory insufficiency, i.e. shock."

For the treatment of the hypotonia of spinal anesthesia, Schuberth recommends inhalation of oxygen and 5 per cent carbon dioxide, because "carbon dioxide causes a rise of arterial pressure by influencing the arterioles."

Here then is evidence as decisive as could possibly be asked that a decrease of the influence of the spinal motor centers upon the tonus of the skeletal muscles results in a decrease in the venous return to the heart, and thus to a decreased cardiac output, fall of arterial pressure, and shock. Certainly in spinal anesthesia muscle tonus is greatly decreased; and in the flaccid muscles the intra-tissue pressure must be correspondingly diminished. Schuberth's observations demonstrate the resulting decrease of the venous return to the heart.

SPINAL SHOCK

A fourth piece of evidence indicating the dependence of the venous return upon muscle tonus is afforded by spinal shock.

This condition results when a man's back or neck is broken, or when the spinal cord of an animal is cut across. The connection between the brain and the centers in the cord is thus severed; and the influence of the higher centers upon the lower is abolished. It is the effects of this severance upon the hind end of the animal that are particularly interesting.

The general character of these effects is the same in all animals: frog, cat, dog, monkey and man. But the degree of these effects is widely different. It varies with the degree in which the higher centers have acquired domination over the lower, and the lower have lost the capacity for independent activity: the greatest degree in man and the least in the frog.

In the frog the spinal centers soon recover sufficiently to maintain the tonus of the parts of the body that they innervate; and the two ends of the animal from then on lead partially independent lives. In a cat, if artificial respiration is maintained, a considerable degree of tonus soon returns. In a dog the return of tonus is slower; and in a monkey much slower. In a man any considerable degree of return may take as many days as it does minutes, or even seconds, in a cat. Indeed death generally supervenes.

In all five of these animals the circulation is depressed and recovers in close agreement with muscle tonus. In none of them is there any good reason to suppose that the vasomotor nervous system is primarily involved. The evidence indicates rather that with the abolition of muscle tonus the venous return is diminished to a point that is generally fatal for man; and that the reason a decapitated cat, on the contrary, soon reestablishes a nearly normal circulation, is that muscle tonus is quickly recovered and with it the venous return to the heart is restored.

Of the venous system much is still to be learned. Measure-

ments of venous pressure are far more difficult to interpret than are those of arterial pressure. The volume of the venous stream is more important than its pressure. Pressure and volume may vary together, as in health; or inversely, as in valvular heart disease. The intramuscular tonic pressure is certainly not the sole factor in the venous return; for it is not alone of sufficient force to drive the blood from the legs to the heart when a man is standing. But its importance is shown by the fact that, when this factor fails, the blood stagnates in the tissues, and the circulation stops.

TWO CIRCULATIONS

The conception of the venous return presented in this and preceding chapters may be made clearer by comparing the circulation of the blood to the circulation of water on the surface of the earth and in the atmosphere.

In the circulation of water the entire energy is supplied by the sun, which by its heat lifts the water to the clouds. In the living body the entire energy of the circulation is supplied by the heart which lifts the blood from the low pressure of the veins to the high pressure of the arteries. As the winds distribute the clouds and rain, so the nervous control of the arteries distributes the blood.

If the rain falls on mountains the water runs down toward the sea with sufficient energy to turn mill wheels and turbines. If, on the contrary, the rain falls on a low-lying plain or swamp, its energy is gone and it merely seeps back to the sea. If the seas were small, all the water would ultimately stagnate in swamps and the return to the sea would cease. There would be no more circulation of water through clouds and rain.

Similarly, if muscle tonus is high and the intra-tissue pressure

throughout the body is considerable, the flow of the blood through the veins brings a full supply to the heart. If, on the contrary, muscle tonus is low and the tissues flaccid, the flow back to the heart is sluggish and the venous return deficient both in pressure and volume. The output of the heart is correspondingly decreased and the circulation fails.

Such is the condition in hypotonia, now called shock.

Chapter XVI

ASPHYXIA BY FAILURE OF THE CIRCULATION

THE most disputed feature of the hypotonia, called shock, is the alteration in the chemical condition of the blood. This state of the blood is perhaps also the most fundamental feature of that state. Yet its relation to the failure of the circulation is obscure.

When I first found (about 1904) that the blood in shock contains much less than the normal amount of carbon dioxide, essentially as Mosso had found in mountain sickness, I followed him in calling the condition "acapnia." I regarded it as due to overbreathing. Later I thought (1910–1917) that acapnia might decrease the volume of the circulation so far that the venous blood would contain little or no oxygen. And when experiment proved this to be the case, I concluded that "asphyxiyal acidosis" must develop. This idea was based on the classic observation of Araki (1894) in Schmiedeberg's laboratory that in carbon monoxide asphyxia considerable amounts of lactic acid appear in the blood and urine. Asphyxia was considered to be largely an intoxication by the acid products of incomplete oxidation.

In 1917 Van Slyke introduced his celebrated apparatus. What this apparatus determines is the amount of carbon dioxide that can be obtained from a sample of blood. Yet the analyses made with it were interpreted as indicating a diminished "alkaline reserve" rather than a low carbon dioxide. And a lowered alkali was taken to indicate that a corresponding amount of acid had been thrown into the blood. The doctrine of "acidosis" in

the sense of an intoxication by acids then dominated public opinion.

Thus a finding of diminished carbon dioxide in the blood, if interpreted as "acapnia," had one implication; but, if interpreted as "acidosis," it implied something quite different. As both these implications are disputable, I have suggested as a substitute for them (in chapter III) a term that merely denotes a fact. That term is "acarbia." It means no more than that the alkali bicarbonates, in which form the greater part of the carbon dioxide is held in the blood, are diminished. It has no implication as to the cause or mode of the diminution. That the carbon dioxide is diminished is a fact on which all investigators agree. The other feature of "acidosis"—low pH—should be called hyperhydria. Its immediate cause is depression of the respiratory center, a relative increase of the H_2CO_3 in the blood and an abnormally high H ion concentration.

Acarbia occurs under many conditions. It is a feature of traumatic shock, asphyxia of the newborn, mountain sickness, carbon monoxide asphyxia, nephritis, diabetic acidosis, post-alcoholic and postanesthetic depression and a number of other conditions. But it may well be that there are several different kinds of acarbia of different origin and meaning. What, in the case of traumatic shock, is the meaning of acarbia?

WOUND SHOCK

By the third year of the war (1917) the trenches of the Western Front had become so stabilized that Cannon and a number of other physiologists were able to make observations on wound shock and related topics. No splanchnic congestion was found. The similarity of shock to hemorrhage was shown to consist in a decrease of the volume of blood in active circulation—termed

oligemia or exæmia—because of a stagnation in the capillaries of the tissues. Although vasomotor failure was also invoked, it was recognized that the crucial factor in the lowering of arterial pressure was the diminished output of the heart and that it was induced by an inadequate venous return. This was exactly what I had found in the laboratory, although in the hurry of war Cannon interpreted his observations as contradicting mine.

Acarbia was also found in all cases of wound shock, but was interpreted as "acidosis." And a warning was issued against the administration of carbon dioxide even by rebreathing, as Porter on one ground, and I on another, had suggested. The reason alleged against the use of carbon dioxide was that "any action increasing acidosis is to be avoided."

Yet when, in Professor Bayliss' laboratory, at University College, London, enough acid was injected into the circulation of an animal to induce a very marked decrease of the bicarbonates of the blood, the conclusion reached by a committee of British and American physiologists was that "simple acidosis, in the sense of a reduction of the alkali-reserve of the blood, even though it be severe and prolonged, does not cause shock or, indeed, any perceptible impairment of the circulation or other vital functions in an otherwise normal animal at rest."

Meanwhile Haggard and I had also tried injecting acid into the circulation. We found that, if carbon dioxide were administered to an animal in that type of acarbia, it was definitely harmful and might even produce death. On the other hand, we found that, when carbon dioxide was administered to animals which had developed acarbia as an accompaniment of shock, the general condition of the animal improved. And most striking was the fact that under inhalation of carbon dioxide a normal amount of alkali was recalled to the blood.

RESUSCITATION FROM POSTOPERATIVE DEPRESSION

Accordingly Haggard, Coburn and I undertook similar observations on patients. We compared those that after surgical operations received no carbon dioxide with those to whom we now for the first time administered an inhalation of this gas mixed with air. The results in the two groups of cases are exemplified in the following comparable protocols.

Anesthesia and operation without subsequent inhalation of carbon dioxide

W. M., man, aged 34; double hernia; ether administration, sixty minutes.

Time minutes	Arterial pressure mm. of mercury	
..	132	Before operation
0	...	In bed, after operation
5	120	Gasps and apneas; cyanotic
25	...	Vomiting
30	108	Depressed respiration; cold, cyanotic, pallid skin
55	102	No improvement
65	...	Vomiting
80	110	Signs of returning consciousness

Nausea for many hours.

Anesthesia and operation with subsequent inhalation of carbon dioxide

S. S., man, aged 46; double hernia; ether administration, seventy minutes; postoperative administration of carbon dioxide.

Time minutes	Arterial pressure mm. of mercury	
..	136	Before anesthesia
0	120	In bed, after operation
1	...	Inhalation of 10 per cent CO ₂ begun
2	...	Marked respiratory augmentation
3	136	Breathing 35 liters of air per minute
4	160	Inhalation reduced to 6 per cent CO ₂ warm, pink skin; sweating
31	...	CO ₂ stopped; patient fully conscious, but emotionally unbalanced; crying; wanted to get out of bed
33	132	

No nausea, vomiting or gas pains; an uneventful recovery.

Most of the operations that we followed were laparotomies for the removal of the appendix or the gall bladder. Anesthesia was administered by the "open" ether method. Often the patient struggled and overbreathed before he was "brought under." During the operation apnea sometimes required the surgeon to stop while artificial respiration was administered. The operation and anesthesia usually lasted for one to two hours. The patient, in a state of extreme flaccidity, was then removed from the operating table to his bed and left in the care of a nurse to recover from the anesthesia without further observation or aid by surgeon or anesthetist.

For us, on the contrary, interest began at this point; and I have still, eighteen years later, a vivid recollection of the gruesome picture that patients then generally presented in the post-operative period: cyanotic, pallid or grey, with empty veins and no pulsation in the jugular, lowered arterial pressure, weak pulse, and a volume of breathing barely half the normal. It was always an hour, and often two or three, before consciousness returned. During this period, and long afterward, the patient was nauseated, vomiting and retching. Persistent hiccup, gas pains, and pulmonary complications with "threatened pneumonia" were common sequelae.

No one then realized that the postoperative and postanesthetic hours were a period of asphyxia as definite and as harmful as a sub-fatal poisoning by carbon monoxide.

In marked contrast was the picture presented by 25 patients to whom we administered inhalations of 5 to 8 per cent of carbon dioxide in air. Their respiration increased to such volumes as they would have breathed under vigorous physical exertion. The greater part of the ether was rapidly ventilated out of the blood; and within a quarter, or at most a half, hour they were

conscious and hilarious or angry as if from alcohol. When the inhalation was stopped, they generally fell asleep.

Immediately after the operation, arterial pressure was usually from 5 to 15 mm. below the patient's normal level, and tended to fall further. Under the inhalation, on the contrary, it rose 10 or 20 mm. sometimes even 30 or 40 mm. within four or five minutes. After termination of the inhalation arterial pressure soon returned to the patient's normal level. It never fell appreciably thereafter. And neither in the cases observed then, nor in thousands that have received such inhalations since in numerous hospitals, has a single case of heart strain ever been reported.

Two of the most striking features noted in the patients who received this inhalation were the rapid recovery of a normal pink skin color and the refilling of the superficial veins. The venous pulse in the jugular also returned and afforded a sign by which we adjusted and limited the strength of the carbon dioxide. We aimed to afford a full venous return without overloading the right heart. Nausea and vomiting were absent or slight. Thirst was lessened. Gas pains occurred in none of the patients to whom we administered the inhalation; and normal bowel movements soon returned. None were "threatened with pneumonia."

POSTOPERATIVE ACARIA

In addition, we were able to show that so far from exacerbating an acidosis, inhalation of carbon dioxide recalls alkali to the blood in patients after operation exactly as we had found to be the case in animals under experiment. The inhalation was administered to four patients after major abdominal operations; two were excisions of 150 centimeters (5 feet) of intestine, one a fibroid tumor and one an appendicitis. Samples of blood were

drawn (a) before the operation, (b) at the end of the operation and (c) after 30 minutes of inhalation of carbon dioxide in air. The samples were equilibrated with air containing 5.6 per cent of carbon dioxide, and the content of this gas in volumes per cent—as an index of their content of alkali—was then determined. The results of these analyses are shown in table VIII.

From these and similar observations on other patients and many animals three inferences follow: The first is that inhalation of carbon dioxide after operations promotes recovery of

TABLE VIII

Showing the bicarbonates in the blood (a) before operation, (b) after operation, and (c) after inhalation of carbon dioxide

	A	B	C
Case 1	53	48	58
Case 2	56	42	57
Case 3	56	48	64
Case 4	59	52	61

vitality, restoration of the circulation, and recall of alkali to the blood.

The second is that the acarbia of postoperative hypotonia is not of the acidotic type. If it were, the inhalation of carbon dioxide would be harmful instead of beneficial.

The third is that postoperative hypotonia resembles asphyxia by carbon monoxide (discussed in chapter VI), both in the occurrence of acarbia and in the benefits induced by inhalation of carbon dioxide.

HEMORRHAGE AS A FORM OF ASPHYXIA

Hemorrhage presents some of the most important problems of surgery; particularly war surgery. Yet in May 1919 the

British Medical Research Committee felt compelled to report that it was uncertain as to "the relative values of blood and (acacia) gum-saline solutions for the replacement of blood lost from the circulation."

The uncertainty hangs on the question whether low arterial pressure, due to deficiency of blood volume, is the sole important condition after a serious hemorrhage; or whether deficiency of the blood gases is also of critical effect. Those physiologists who have figured the problem of shock in terms of "vasomotor failure" have commonly adopted the first of these alternatives; for shock and hemorrhage are much alike. Those, on the contrary, who think rather in terms of oxygen consumption, oxygen deprivation and asphyxia are more inclined to a broader view. They hold that the loss of red corpuscles and the consequent decrease in the capacity of the blood to carry oxygen to the tissues are the ultimate cause of death after hemorrhage. They find support for this opinion in the fact that the effects of hemorrhage upon respiration are as marked as those on the circulation. Neither opinion excludes the other. As a basis for treatment it is vitally important to determine whether any artificial fluid containing no oxygen carrier can really take the place of blood and its hemoglobin.

Among surgeons there is no such division of opinion. They demonstrate their acceptance of the respiratory, in contrast to the purely circulatory, conception of hemorrhage by using transfusion of blood rather than infusion of gum-saline or any other solution. They thereby recognize by implication that to a large extent hemorrhage is a form of asphyxia. Yet this recognition is not complete. Neither the ambulances nor the emergency receiving rooms of our hospitals are as yet equipped with cylinders of oxygen and nasal catheters for the administration of

the gas to exsanguinated patients while their blood is being typed.

The literature of transfusion is enormous; 453 papers and books were listed in Amberson's review of "blood substitutes." Many investigators have demonstrated that with the infusion used the subjects, men or animals, revived and survived. But they frequently fail to demonstrate also that the subjects would have succumbed without the infusion. How long the subjects survive is also important. An exsanguinated man or animal exhibits striking improvement from infusion of a mere saline solution; but the benefit is brief. The probability of death within 24 hours is not thereby appreciably lessened.

With these considerations in mind Haggard and I directed a sufficiently extensive investigation of hemorrhage to afford roughly statistical results. The work was done during the last year of the war (1918) by a squad of young "Ph.Ds. in khaki" assigned to our command by Colonel F. F. Russell. At least two members of that squad, S. R. Detwiler and W. H. Taliaferro have since made outstanding contributions to other fields of medical science.

The dogs used were protected from fear by gentleness and petting, and from pain by means of novocaine. A standard degree of hemorrhage was established: a quantity of blood equal to 0.25 per cent of the body weight was withdrawn each 5 minutes until the arterial pressure fell to about 28 mm. The amount of blood drawn varied from 3.8 to 5.8 per cent of body weight. It was found that if the animals were then left to themselves the chances were equal that any one of them would die or survive. All those that were bled even slightly less (i.e. to a higher arterial pressure) survived to the next day, and were then improving. All those that were bled to even a slightly greater degree (i.e.

to a lower arterial pressure) died within a few hours. The results are shown in table IX.

In these experiments it was especially noteworthy that while infusion of saline improved the vitality of the subjects for a half hour, or at most an hour, infusion of acacia gum-saline bicarbonate solution was beneficial for several hours. But the probability that life would be prolonged for 24 hours was not im-

TABLE IX
Showing the effects of various treatments after a standard hemorrhage

	NUMBER OF CASES	DIED	LIVED
Controls, no infusion or inhalation	15	8	7
Intravenous infusion of sodium chloride solution equal in volume to the blood previously withdrawn.	8	3	5
Same volume of 2 per cent sodium bicarbonate.	6	1	5
Same volume of solution of gum-acarbia in 2 per cent sodium bicarbonate.	6	4	2
Morphine, 0.2 gr. per kilo	5	3	2
Morphine and saline, as above	3	1	2
Inhalation of carbon dioxide.	7	7	0

proved by either solution. In contrast to this finding there can be no doubt that if blood had been infused up to the volume that had been lost, barring accidents, there would have been 100 per cent of recoveries. Evidently, apart from the loss of fluid, which the mere drinking of normal saline could as well have replaced, the cause of these deaths from hemorrhage lay in the loss of the red corpuscles. Such loss is in large part analogous to the loss of oxygen carrying power induced by carbon monoxide. The blood plasma may be largely replaced by artificial fluids—as in

modern experiments by Amberson and others on so-called "plasmaphoresis." But if hemorrhage is not to induce asphyxia, the replacement of corpuscles is essential: as indeed the practice of surgeons now recognizes.

In support of the view that death after hemorrhage is essentially death by asphyxia, our observations on respiration and blood alkali were significant. The volume of breathing—accurately measured by means of a tight fitting mask, double valves and a gas meter—was always increased even by a quite small withdrawal of blood; and each further withdrawal increased it more. Respiration was an accurate index of the severity of the hemorrhage and prognosis could be based on this function quite as well as on arterial pressure. If the hyperpnea increased, death always followed; if it gradually decreased the animal survived.

Accompanying the increase of breathing there was always a development of acarbia: initiated by a fall of the carbon dioxide content of the arterial blood from a level of 40 or 50 volumes per cent before the hemorrhage to 20 or 30 after it was completed. If it fell more, or continued to fall, the animal died; if it fell less the animal usually recovered. The vital importance of the corpuscles of the blood is indicated by the fact that inhalation of carbon dioxide, although it recalled some of the lost alkali of the blood, did not save acutely acarbic animals. In this respect hemorrhage differs both from shock and from carbon monoxide asphyxia. This difference is probably due to the fact that much the greater part of the true reserve alkali of the blood is normally held in the corpuscles in combination with hemoglobin and the loss of corpuscles in hemorrhage therefore induces a state like true acid poisoning.

CONCUSSION

In all the early literature concussion, shock and syncope (fainting) were discussed together. It was only when the Goltz-Fischer vasomotor theory of shock developed, that shock and syncope were no longer compared with concussion and were distinguished from each other. Yet there is certainly a fundamental similarity; the three conditions differ chiefly in duration. A blow on the head without serious injury may render a man unconscious. Bad news may render a woman unconscious. The older writers recognized that similar effects imply similar causes.

Concussion is easily demonstrated on animals. The common housefly is quite susceptible. If one is struck with a folded towel or newspaper it may fall as if dead and may lie for a time completely inert. Then it may "come to life again" and fly away as well as ever. The biologist Romanes observed that a jelly fish (medusa) may act similarly. If one of these animals, while making vigorous swimming movements, is lifted out of the water and placed on a blacksmith's anvil, which is then struck heavily at another point with a hammer, all movement ceases. Replaced in sea water the animal floats for a time relaxed and inert. Then movement returns and no sign of permanent injury appears. Many a boy shooting frogs has noticed that it is not necessary that the bullet of his small rifle should strike the frog. If it strikes in the water nearby, the frog becomes limp and motionless. Sometimes it is dead; but sometimes not. It must be captured soon; for otherwise it may swim or hop away as well as ever. When a lake or river is dynamited, the fish nearby are killed; but those at a distance, after a period of concussion shock generally recover.

What is it that temporarily occurs in all these cases? Obviously the nerve centers, and particularly the motor and tonic

centers, cease to act. In such conditions, as Sherrington has shown, a block develops at the synaptic junctions of the neurones. Impulses no longer pass from one neurone to another. It has even been suggested that as the dendrites, or pseudopodia, of an outgrowing neurone may retreat and become motionless under abnormal irritation, conduction might be thus interrupted; but some chemical block is now considered more probable.

Whatever the nature of the block, this is true: under many forms of abnormal, painful, or injurious irritation of the body, the motor and tonic centers in the nervous system cease to act. Muscular tonus is abolished. The individual falls flaccid. The intra-muscular and intra-abdominal positive pressures are largely abolished; and to a considerable extent the intra-thoracic negative pressure also. The blood stagnates in the tissues. The venous return is diminished. And as the output of the heart is correspondingly diminished, arterial pressure also falls.

Such a conception of concussion would probably meet with little objection. No one has ever assigned concussion to "vasomotor failure." The basis of the condition is obviously, not in the sympathetic, but in the central nervous system.

FAINTING

Syncope, or fainting, on the contrary, has for more than fifty years been regarded as a temporary vasomotor depression. There has been no alternative conception.

It is true that a cessation of the blood supply to the brain induces unconsciousness and a relaxation of all the muscles of the body. The person falls limp. But in fainting the primary occurrence might be either failure of the circulation, or failure of muscular contraction. Each would induce the other. Failure of the motor centers and the consequent relaxation of the muscula-

ture of the body stop the circulation quite as effectively as failure of the vasomotor nervous system.

In my opinion, there really is no experiment recorded in the literature of physiology that justifies the belief, now commonly held, that depression of the vasomotor nervous system, merely by lowering arterial pressure, apart from decrease of the venous return and the output of the heart, can induce a sufficient failure of the circulation to account for fainting. Unless men and women are very different in this respect from dogs and cats, neither section of the splanchnic nor complete excision of the sympathetic nervous system would have so great an effect. On the other hand, a sudden decrease in the venous return and in the output of the heart has this effect.

The effect of a sudden decrease of these functions can be shown by Valsalva's experiment. In a certain college the students a few years ago had for a time a fad for performing the following experiment. The subject was told to draw a deep breath, close his mouth, and hold his nose. The operator, standing behind him, then suddenly squeezed his chest and the subject dropped to the floor momentarily limp and unconscious. The venous return was stopped by the pressure in the chest. But this experiment should not be repeated; for air may be forced into a pulmonary blood vessel and cause a fatal embolism. Such fatalities have in fact occurred in men who have held their breath until they reached the surface of the water after escaping from a submarine.

All that I intend here is to point out that when bad news, or bad ventilation, and prolonged standing induce fainting, it may well be because the motor centers in the spinal cord fail to maintain the tonic contraction and intra-tissue pressure in the skeletal musculature. The venous return is decreased and the output of

the heart also. This is much more likely than the conventional explanation of fainting by "vasomotor failure."

CONGESTIVE HEART FAILURE

When the heart is so damaged that it fails to pump a sufficient volume of blood to supply fully the demands of the tissues for oxygen, various degrees of asphyxiation develop. In some respects such asphyxiation resembles that induced by carbon monoxide; in other respects it is more like that after an extensive hemorrhage; and in others again it differs from both, but reproduces the conditions seen in mountain sickness and in partial acclimatization to great altitudes.

So long as the heart is able to compensate for its defects, and to pump a normal volume of blood during rest, no disturbance of respiration is induced. It is only when physical exertion increases the demand for oxygen beyond the capacity of the heart to supply, that the man experiences respiratory distress.

If compensation is a little less than perfect during rest, the slight anoxia induces at intervals a sigh, or mild anoxemic gasp: a single deep inspiration. If compensation is more incomplete, rhythmic alternations of overbreathing and underbreathing may occur. In this Cheyne-Stokes respiration the hyperpneic periods are induced by the deficiency of oxygen, which the increased breathing then temporarily counteracts. But the gain in oxygen is obtained only at the cost of a temporary acapnia, which then induces a period of diminished breathing, and a return of anoxemia. In more developed cases the patient is continually more or less acapnic. This interaction of anoxemia and acapnia is particularly distressing at night. He no sooner drops asleep than apnea sets in; anoxemia becomes acute; and he starts up terrified by a sense of suffocation.

The interaction of anoxemia and acapnia in such cases is further demonstrated by Pembrey's finding that Cheyne-Stokes breathing can be relieved by inhalation of either oxygen or carbon dioxide. Inhalation of either gas, or in some cases mere rebreathing into a bag for a few minutes after getting into bed, may enable the cardiac patient to get to sleep without the occurrence of apnea, and the consequent partial asphyxiation.

The similarity between such patients and healthy men acclimatized to altitude is further shown by the considerable increase of the red corpuscles in the blood of both. Continuous oxygen inhalation is shown by Barach and others to be beneficial.

In one respect, however, congestive heart failure differs from most of the other forms of asphyxia. Instead of an inadequate venous return such as occurs in hemorrhage, valvular disease of the heart may involve acute venous congestion. Instead of an insufficient venous supply to the heart, the supply is superabundant; but the heart is incapable of pumping it onward. In X-ray pictures of the chest the heart, or rather its content of blood, is found to be abnormally large in congestive heart failure; but it is abnormally small and empty after hemorrhage and in hypotonic shock.

In both the hemorrhagic and the congestive forms of circulatory failure the development of asphyxia is signalized by violent overbreathing and so-called "air hunger." (Failure of the circulation of this type has recently been investigated by Harrison. Unfortunately his subjects were narcotized with barbiturates, which abolish the normal control of respiration.)

FACTS AND POSTULATES

From the comparison of the various forms of asphyxia, presented in this and preceding chapters, two new conceptions have

been developed. One is that of muscle tonus as a major factor in the control of the circulation, and of failure of muscle tonus as a cause of failure of the circulation. The other is that of "acarbia" as induced by "hyperpnein," in place of "acidosis" induced by lactic or other acid. In presenting these conceptions I have tried to keep clear what parts are facts, and what parts are postulates. This distinction will, I hope, prevent these conceptions from becoming dogmas; but will instead, facilitate confirmation of the facts and correction, by further investigation, of any errors that may be involved in the postulates.

Chapter XVII

MUSCLE TONUS AS A FACTOR IN ARTIFICIAL RESPIRATION

IN THE year 1912 two types of accident excited to action the authorities concerned. The National Electric Light Association was faced with the problem of what should be done for men who receive a heavy electric shock. The Bureau of Mines, then newly organized, found that among the major hazards of coal mining one of the most serious was asphyxiation by carbon monoxide. Electric shock also occurs in mines.

Accordingly, as described in chapter VIII, both organizations asked a Commission to visit a big electric power station, and to go through some coal mines in Pennsylvania; and then to investigate the subject of resuscitation. In particular we were to recommend the best procedure for administering artificial respiration. As it was a rather large Commission, the experimental investigation was carried out by a sub-committee consisting of Dr. W. B. Cannon, Dr. S. J. Meltzer and myself.

THE PULMOTOR AND SIMILAR APPARATUS

We had first to deal with that imposing, but really foolishly designed apparatus—in practice almost valueless and sometimes probably harmful—the pulmotor. At best it merely supplies air with a small enrichment of oxygen. I had already seen the pulmotor in operation. It was on a case of carbon monoxide asphyxia. The man, although unconscious, was breathing naturally, and needed no artificial respiration. The pulmotor was running; but its strokes were entirely out of step with the breathing, which it was impeding rather than aiding. After

full consideration the Commission unanimously disapproved the pulmotor; and this action virtually ended its general introduction in this country. Yet the idea of an apparatus, that—supposedly—would maintain life by machinery, appeals so strongly to the love of the miraculous in the public mind that similar devices under other names still find purchasers. The magical word has also continued in popular use; and any device for resuscitation is even now often referred to as a “pulmotor.”

The main argument offered for all such appliances as the pulmotor, lungmotor, so-called resuscitators and others, is a demonstration of their capacity alternately to inflate a rubber bag (simulating the lungs), and then to suck it flat. The reversal from blowing to sucking is automatically induced by the resistance of the bag when full or empty. Of this feature of such apparatus the Commission reported:

“Inflation and deflation of a bag is deceptive, because the bag, unlike the air passages of the body, offers no resistance till full. As soon as the inspiratory blast meets an obstacle in the air passages, however, it is automatically cut off and turned into expiration; and thus frequently no efficient inspirations are performed. . . . The second harmful factor brought out by these experiments is the performance of expiration by suction. In normal respiration expiration is accomplished by a power that does not suck, but drives out the air by the elasticity of the distended or compressed tissues, aided, sometimes, by muscular contraction.” . . . And from various lines of investigation in laboratory and clinic, the conclusion was reached that “the automatic mechanism of the pulmotor, although an ingenious technical contrivance, instead of assuring artificial respiration, may interfere greatly with its efficiency, because the mechanism is liable to cut off inspiration prematurely.”

In this verdict two other committees of investigation, one in 1918, the other in 1921, unanimously concurred. Evidence, which I have more recently obtained from obstetricians who have tested a recent pulmотор—a so-called resuscitator—on asphyxial or deeply narcotized babies, is to the effect that it frequently merely “clicks” from inspiration to expiration and back to inspiration in rapid succession without producing any movement of air in or out of the lungs. In some cases, also, autopsy has shown definite injury to the lungs.

The Drinker respirator is in an altogether different class. Although this apparatus is not, in my opinion, suited to resuscitation in emergencies, it is often of life saving value in cases of prolonged respiratory paralysis. General experience with the Drinker respirator also affords valuable evidence on what artificial respiration apparatus should do, and what it should not. This experience indicates that the action should be confined to a succession of inspirations, and should not include forced expirations. When the body is enclosed in the Drinker respirator negative pressure induces inspiration in essentially the same way as does positive pressure over the face with apparatus of the pulmотор type. In the Drinker respirator forced expirations by positive pressure are now generally omitted. Artificial respiration confined to inspirations, either with the Drinker or the pulmотор type of apparatus, if not too forcible, can do no harm; but forced expiration with either type of apparatus can. If then, the principal objection to any pulmotor, resuscitator or similar device is to be removed, negative pressure should be omitted. It should be added that, among the cases upon which so-called resuscitators have been used, the latest to come to my knowledge is one in which a child had to be removed for a time from a Drinker respirator. During this time the resuscitator was substituted; but the child died.

MANUAL METHODS

While Cannon studied apparatus and Meltzer developed insufflation, I investigated the various forms of manual artificial respiration, and particularly the prone pressure method, then recently introduced by Schafer. This investigation first gave me an insight into the importance of muscle tonus for respiration and later for the circulation.

No method is better than the way it is used. To determine the efficiency of the various methods of artificial respiration, I introduced them into the work of the students in my laboratory course. In particular the prone pressure method was applied by each student to another, and compared with other manual methods. The volume of the pulmonary ventilation induced was measured by means of a close fitting mask, from which the expired air passed to a gas meter. The results afforded a highly significant discovery. We found that the volume of air, thus artificially breathed, was in all cases and by all methods, if continued long enough, almost exactly the same as that of natural breathing: never appreciably more, never appreciably less.

This observation was at first very surprising. Then the explanation was found. It is that in normal men under artificial respiration the respiratory center still regulates the tonus—and therewith the elasticity—of the thoracic muscles and diaphragm. The degree of tonus is so regulated by the subject's own nervous system that, after each artificial compression, the chest expands again to a certain volume; and this volume is, on the average, that which affords precisely the amount of pulmonary ventilation that the man needs to supply oxygen and remove carbon dioxide. It is the tonus of the respiratory muscles, especially the diaphragm, that induces inspiration during manual artificial respiration; and the respiratory center under the influence of the blood gases controls their tonus.

In order to test this explanation, the subjects were next directed to perform voluntary overbreathing for a couple of minutes. Because of the acapnia thus induced, they then breathed subnormally for a time, or even stopped entirely. And, when any form of manual artificial respiration was applied during this period of apnea, it was always found that much less than the normal amount of air was moved out of the chest, and correspondingly little was drawn in. The tonus of the respiratory muscles was diminished; and the re-expansion of the thorax, after each compression, was correspondingly diminished.

To throw further light on this matter, I then performed such experiments as the following: A cat was placed under moderate chloroform anesthesia; its trachea was connected with a small spirometer; and the amount of air breathed in a minute was recorded. A fatal dose of chloroform was then quickly administered; and respiration and the heart action were thus stopped finally. The trachea was again connected with the spirometer; and artificial respiration was performed by squeezing the thorax for a moment, and then releasing the compression. At first a nearly normal volume of air was expelled from the lungs by each artificial expiration; and when the pressure upon the thorax was released, the same volume of air was drawn in again. As the animal made no spontaneous effort to breathe, this inspiration was entirely due to the tonic elasticity of the thoracic muscles and diaphragm.

This condition was brief. As the nerve centers gradually failed under asphyxia, and their influence on the muscles faded out, the tonic elasticity of the thorax was correspondingly abolished. Less and less air was expelled by each succeeding compression; and less and less was drawn in each time that the compression was released. Finally, after ten or twelve minutes,

when the body was entirely flaccid, there was no movement of air whatever. Compression of the thorax by the operator's hands then caused no air to be expired; for the chest was already deflated. And no air was drawn in; for, with the entire loss of tonus, the elastic recoil of the muscles was abolished.

Such observations on men and animals showed that the respiratory center and the motor centers in the spinal cord strongly influence the muscular tonus of the body. In particular the respiratory center determines the tonic elasticity of the diaphragm and other respiratory muscles; and it continues to exert this control, even when natural breathing has ceased. Under artificial respiration the operator does the work of compressing the chest and squeezing air out of the lungs; but the residual elasticity of the victim's own muscles determines the extent to which the chest will re-expand, and draw air into the lungs again, when the pressure is relaxed.

Against the prone pressure method, as described by Schafer, it has been alleged that the manipulation causes only expiration, and does not aid inspiration. To meet this objection I recommended that the arms of the victim should be brought forward, until they are parallel with his neck and head—the most extreme inspiratory position attainable; and that one arm should be bent at the elbow, with the hand on the other arm and the head resting on the bent forearm. It was my conclusion 25 years ago, and on the basis of much experience since it is my opinion still, that with this modification the Schafer method does all that it is possible to do by means of manual respiration. It is impossible by any manual method to induce a greater degree of respiration than the tonus of the patient's own muscles produces. The claims that other methods do more for inspiration are all fallacious, because based on observations on normal men. The prone

pressure method is most easily applied, and can be continued longer than any other procedure. It is therefore best. It also aids the circulation by pressing blood from the abdominal vessels toward the heart.

It is estimated that, since the Commission made its report, 13,000,000 policemen, firemen, boy and girl scouts and others have been trained in the prone pressure method.

ARTIFICIAL CHEYNE-STOKES BREATHING

During the summer of 1913 I spent a few weeks in England with Haldane to attend the International Medical Congress in London; and I told him of my observations. As he was not convinced that the experimental "victim"—instead of the operator—determines the amount of pulmonary ventilation, I invited him to "resuscitate" me. First, I overbreathed vigorously; and when I had become completely apneic, he started rhythmic pressures on my back. Now it happens that I am very sensitive to even slight deficiency of oxygen, which gives me a "high ceiling," but renders me prone to Cheyne-Stokes respiration; and to his astonishment he found that, although all of his pressures were of the same force and timing, several in succession were effective and then several ineffective: an artificial Cheyne-Stokes respiration. Yet I was quite unaware of what was happening.

TONUS AND ITS FAILURE

Evidently it is the state of the subject, not the technique of the operator, that determines the volume of artificial respiration, as Liljestrand also found. All the tests of the various alleged improvements on the Schafer method, and on other methods, that have been made on men in normal condition, with normal respiratory centers and normal tonus, are valueless as evidence

of the comparative merits of these improvements and methods. All such tests on normal men would, if continued for 10 or 15 minutes, give an exactly normal pulmonary ventilation. Forceful pushing or squeezing on a normal person—or imitation victim—causes him to show a little more artificial respiration for a minute or two; but his respiratory center soon reasserts its control, and prevents the operator from inducing other hypo- or hyper-capnia. No method can induce for long a pulmonary ventilation in excess of what the residual tonic elasticity of the victim's own muscles affords in their inspiratory recoil from manual compression of the chest. When the tonic elasticity of the muscles ceases entirely the victim is irretrievably lost. His nervous system, which induces the tonus, is by then damaged beyond recovery. Soon after death the thoracic muscles, and particularly the diaphragm, relax completely. For this reason a corpse cannot be artificially respiration to any appreciable degree by any manual method.

That this is true was found also by Haggard who happened to be at hand when a neighbor suffered a fatal "heart attack." At first artificial respiration was effective; but, as the tonus of the body gradually failed, the artificial respiration failed correspondingly. After 10 or 15 minutes no movement of the body—neither pulling nor compression—was in the least degree effective in causing any movement of air in or out of the lungs.

It might be inferred from these facts that an apparatus that would blow air into the lungs would be a more effective means of resuscitation than manual artificial respiration. But here again the tonus of the victim's own muscles sets a limit. Many investigators have tried to induce acapnia by what they supposed was excessive ventilation of the lungs; and have failed. The reason is that, as soon as a slight degree of over-ventilation

is induced under a rapid succession of blasts of air, the tonus of the muscles is so much decreased that, between inflations, only a slight expiration occurs. The use of a bellows on a corpse or dead animal merely induces a generalized emphysema. In spite of the limitations that nature imposes, manual artificial respiration is still the most effective emergency method of resuscitation.

THE LIMIT IN RESUSCITATION

In cases of drowning, the time limit within which resuscitation is possible is generally given as not more than 10 or 12 minutes. The metabolism of the central nervous system requires a constant supply of oxygen; otherwise irreversible changes occur. The heart of a drowned man or animal, if excised from the body and perfused with oxygenated salt solution, can be made to beat again. The heart of a baby can be thus revived even after many hours. But, even if the heart in the body of a drowned man were made to beat again, the lack of muscle tonus, due to failure of the nervous system, would prevent the restoration of the circulation. And, even if the circulation were restored, the brain would be irrecoverably damaged.

An extraordinary naiveté in regard to artificial respiration has long prevailed among obstetricians. A colleague, who has even made important contributions to the management of labor, told me recently: "If the baby does not breathe, I support it in a warm bath and just press on its sternum with my forefinger." In this he makes the common mistake of supposing that, by compressing the still atelectatic lungs of an asphyxial baby, he can draw air into them.

Now, however, in cases of asphyxia pallida, or as it might be better called asphyxia atonica, intratracheal insufflation is com-

ing into use, and may save life when all other measures would fail. The same statement may be made in regard to cases in which respiration fails under spinal anesthesia. Twice in the past year I have had calls for advice from surgical clinics in which this emergency had occurred. In each case life was saved by intratracheal insufflation of oxygen aided by an occasional compression of the thorax. To Meltzer is due the credit for showing that intratracheal insufflation will supply sufficient oxygen; but that it may fail to effect an adequate elimination of carbon dioxide, unless aided in this way.

Subcutaneous injection of oxygen has been proposed as a substitute for inhalation or insufflation; but the rate of absorption is too small to be of any value. And there is risk of a gas embolus.

CARBON DIOXIDE AS A TONIC

The most significant experiment that can be performed to show the nature of the effect that inhalation of carbon dioxide induces is as follows: The volume of air that a man is breathing is determined. He is then subjected to manual artificial respiration; and the volume of his breathing is again determined. It is the same as before. By means of an inhalator pure oxygen is administered both during natural and artificial respiration. The volume of the pulmonary ventilation, as measured by a gas meter, is found to be the same under all these conditions. Then air containing 3 to 5 per cent of carbon dioxide is administered, both while he breathes naturally and under artificial respiration. The same volume of breathing again results from natural and artificial respiration. But these volumes are much larger than was the case without the accessory influence of carbon dioxide.

What do such observations signify? They signify that the

primary effect of carbon dioxide is that of a tonic. The tonus of the respiratory muscles is increased to such an extent, alike under natural and artificial respiration, that the lungs are ventilated with exactly that volume of air that will maintain in the lungs, the blood and the respiratory center exactly that tension of carbon dioxide which the sensitivity of the respiratory center at the time requires.

This tonic effect of carbon dioxide as an accessory to artificial respiration is often of lifesaving value in cases of electric shock and near drowning. In such cases artificial respiration at first moves just enough air to maintain life. Simultaneous inhalation of carbon dioxide increases tonus, and with it the volume of the pulmonary ventilation. Furthermore, the object to be aimed at is not the maintenance of prolonged artificial respiration, but rather to induce natural breathing at the earliest possible moment. It is only under such conditions as those of drowning and electric shock, at places where no inhalator is available, that prolonged artificial respiration should be maintained without accessory inhalation of carbon dioxide.

METHODS OF ADMINISTERING CARBON DIOXIDE

For the administration of carbon dioxide diluted either with oxygen or with air during both natural and artificial respiration, several types of inhalators are employed. Each has a mode of use distinct from the others.

The most widely used apparatus is the H. H. inhalator with which the rescue crews of the city fire and police departments and of the gas and electric companies are generally equipped. The steel cylinders contain a mixture of 7 or 8 per cent of carbon dioxide in oxygen under high pressure. By means of a reducing valve and adjusting needle valve, the gas is allowed to flow into a bag

from which the patient—usually a victim of carbon monoxide—inhales. The mask should be held tight over the face, so that the gas is inhaled without admixture of air. The valves on the mask are so arranged that through one the inspirations are drawn entirely from the bag, while through the other the expirations are discharged into the outside air. There is thus no rebreath-

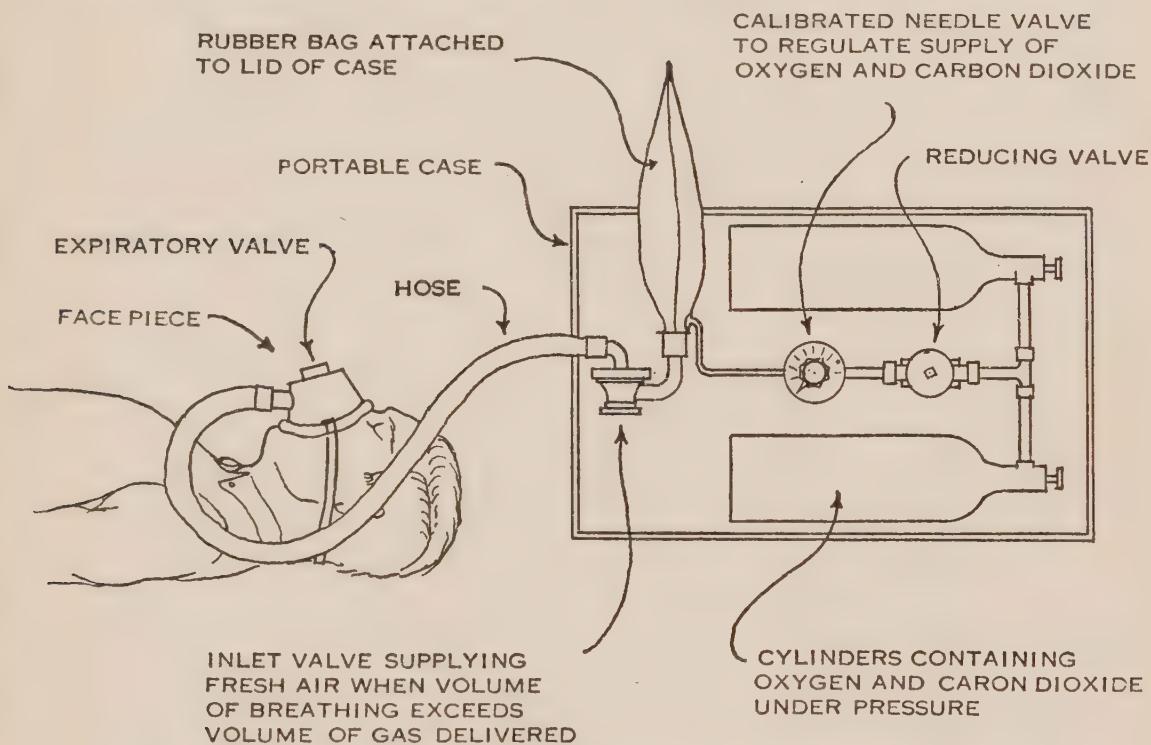


FIG. 11. The H. H. inhalator supplying carbon dioxide and oxygen.

ing whatever. The lungs are flushed with entirely fresh gas at each breath, and the elimination of carbon monoxide is thus expedited.

This form of inhalator is also efficacious on cases of asphyxia neonatorum. A simpler form is, however, quite adequate. It involves merely a cylinder of the gas mixture, a needle control valve, a breathing bag and a tight fitting mask. For the newborn, rebreathing need not be avoided; indeed, it is rather de-

sirable. A mild form of artificial respiration—to replace mouth to mouth breathing—is induced by squeezing the breathing bag intermittently, while the mask is held tight on the face, with the head of the baby in hyperextension, so as to keep the pharynx

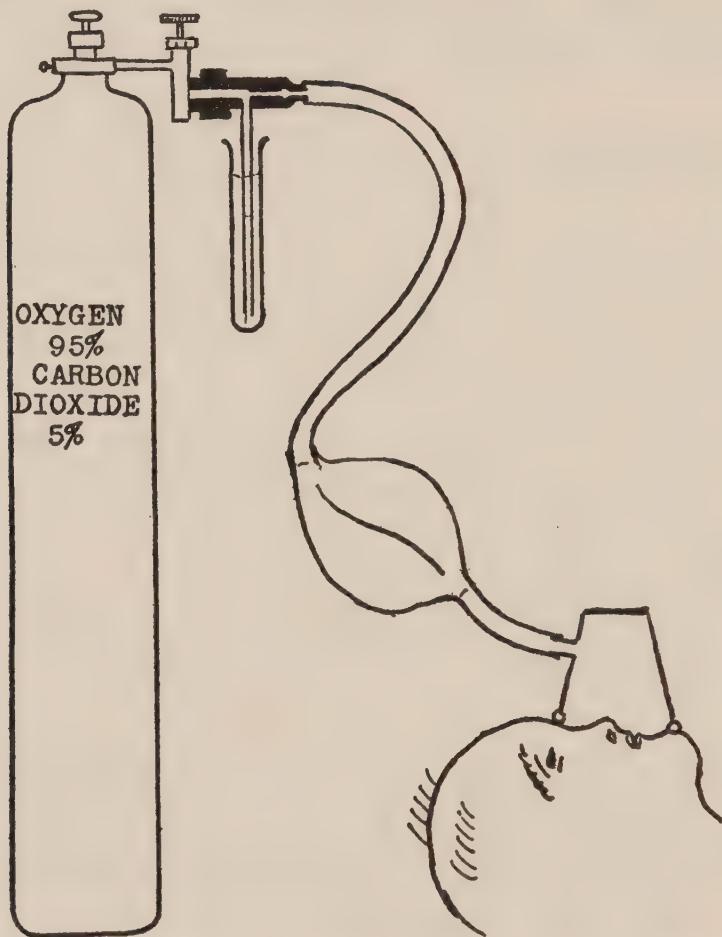


FIG. 12. Infant inhalator supplying carbon dioxide and oxygen.

open. For severe cases of asphyxia, or babies of heavily narcotized mothers, an additional cylinder of 15 to 20 per cent carbon dioxide in oxygen is advisable. As soon as respiration is well started, 7 per cent, or even 5 per cent, is sufficient. In cases of asphyxia pallida, with complete atonicity, the gas mixture should be administered at first by intra-tracheal insufflation.

On most of the anesthesia apparatus now in use, a cylinder of oxygen and another of carbon dioxide are provided; and the anesthetist adjusts the mixture of these and other gases (e.g. ethylene, nitrous oxide, ether, etc.) as the condition of the patient and the demands of the surgeon require. By some anesthetists

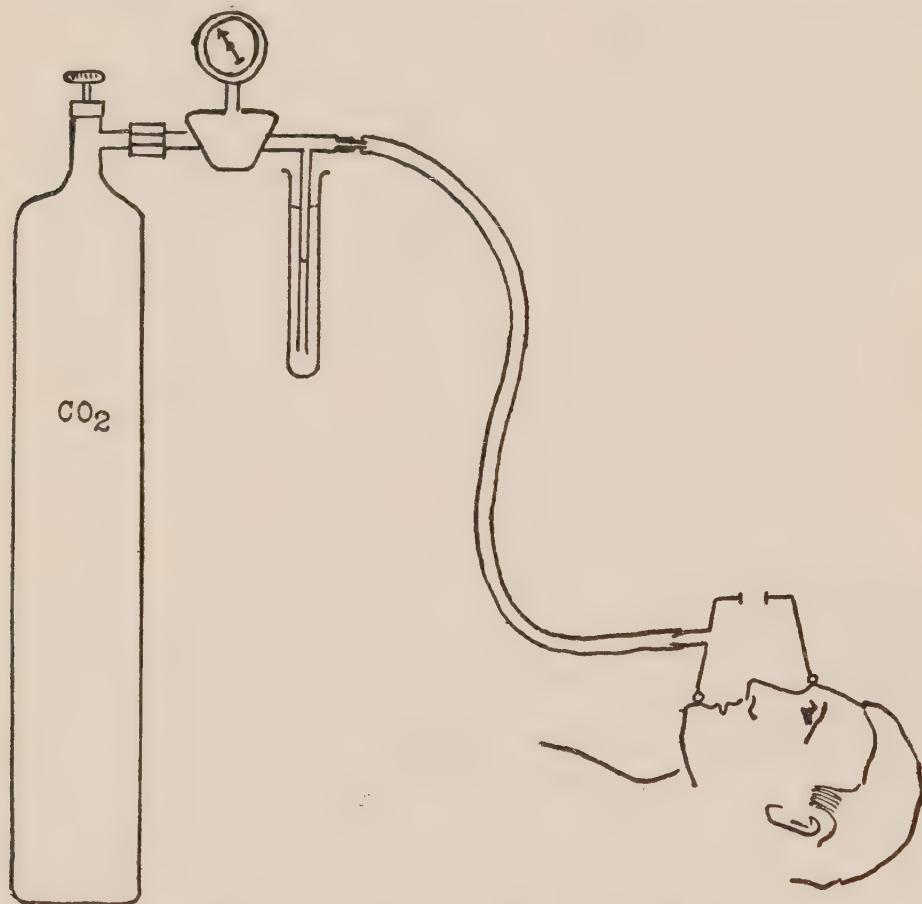


FIG. 13. Inhalator with open mask supplying carbon dioxide to the inhaled air.

carbon dioxide has even been used to excess. Although the deaths charged to this cause were probably due rather to deficiency of oxygen, excessive stimulation of respiration should be avoided. In general, the better the anesthesia, the less this resuscitant should be required.

For many purposes,—e.g. treatment of hiccup and intermittent

claudication, as a substitute for exercise in angina pectoris, prevention of postoperative atelectasis, clearing of the lungs and airways in whooping cough and early pneumonia, relieving the sufferings incident to withdrawal of morphine in addicts, etc.—

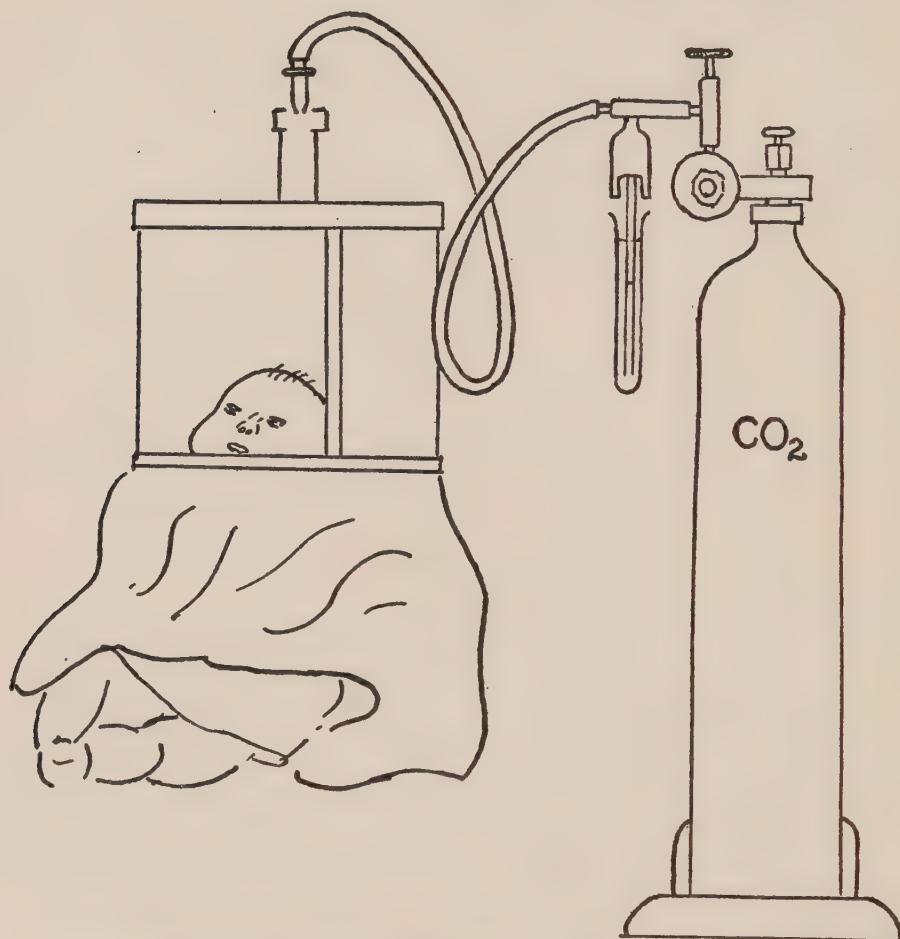


FIG. 14. Infant tent to which a mixture of carbon dioxide and air is supplied through an injector. The upper part is celluloid, the lower part is a cloth curtain. See pages 193 and 285.

it is unnecessary to use the mixture of carbon dioxide with oxygen. Carbon dioxide alone, mixed with the inhaled air, is sufficient. It is also much less expensive, while oxygen, because of its ready absorption at the end of anesthesia, may even promote atelectasis. All that is needed is a cylinder containing liquid

carbon dioxide, a simple reducing valve, an adjustable needle valve connected to a water manometer graduated to show the flow of gas in liters per minute, and to serve as a safety blow off to prevent excess, and finally an "open" or "slotted" mask. The patient is first allowed to breathe air alone through the hole in the top, or slot in the side, of the mask. Then, very gradually, the gas is turned on, so as to mix with the air inspired through the mask. And, as respiration responds, the flow of carbon dioxide is increased, until the depth of breathing is nearly or quite maximal. But the respiratory rate should not be increased.

For children threatened with bronchitis, a small tent should be used; and the carbon dioxide from the cylinder should be passed through an injector, which automatically mixes it with air in a proportion of 5 or 6 per cent of carbon dioxide; or the injector may be attached to an incubator.

RESPIRATORY STIMULANT DRUGS

Down to the time that inhalation of carbon dioxide was introduced as a means of stimulating respiration, the only recourse of the physician lay in the use of his hypodermic syringe. Such drugs as atropin, caffein, strychnine, camphor, cocaine, apomorphine, adrenalin, and even ether were injected; and in recent years such drugs as lobelin and coramain have been used. Occasionally, if the patient was pulseless, the needle was passed through the chest wall into the heart for an injection of adrenalin. If he lived, the saving of a life was claimed. Actually, if the patient recovered with the injection, it is certain that he would have recovered equally well without it, and also without the risk of a pericardial hemorrhage or infection. Such therapy is as unsound as the "counter shock" sometimes applied to the victims of electric shock. Because one shock may stop the vital

machine is no ground for supposing that another shock, either mechanical or electrical, will start it again.

Respiratory stimulant drugs are of very limited value, and may easily be harmful. Respiration is not an independent function. It is closely coordinated with the other activities of the body, physical and chemical, and particularly with metabolism. Any drug that disturbs this relation for more than a brief period seriously upsets the economy of the body. Ether and nitrous

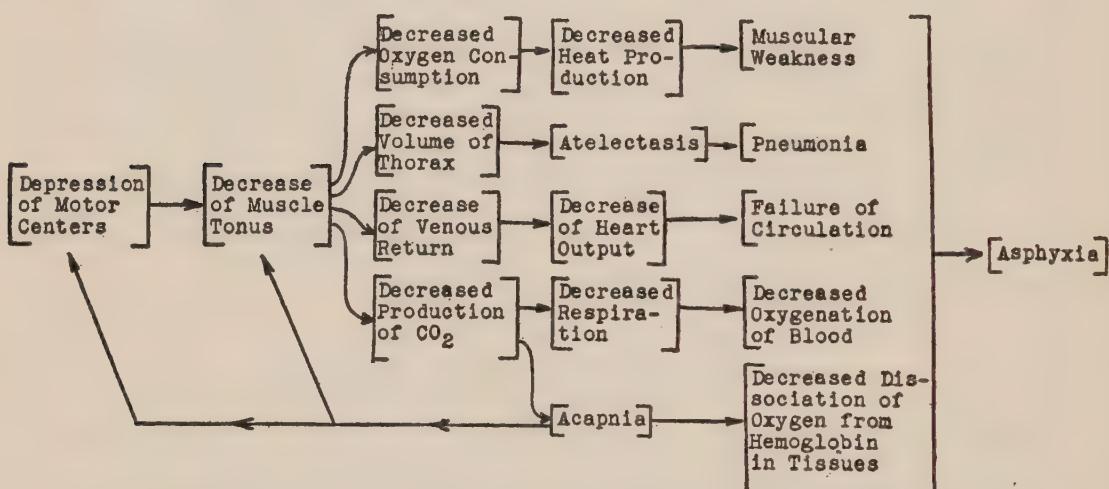


FIG. 15. Showing the causal sequences through which depression leads to asphyxia. Strychnine and especially inhalation of carbon dioxide tend to counteract the earlier stages by increasing muscle tonus, and thereby to break the vicious circle in which depression of motor centers and muscle tonus induces acapnia and acapnia in turn induces depression of centers and muscle tonus.

oxide in the first stage of anesthesia may induce a large increase in breathing. But, as metabolism is not correspondingly increased, the result is an acapnia which may lead to a fatal apnea. A wide variety of other substances, even in small doses, may also increase respiration. Such substances as cyanides, sulphides, salts of monoiodoacetic acid and many others may induce overbreathing, together with other effects that are even more undesirable.

In contrast to such drugs of brief and powerful action are a few that act largely upon and through metabolism. The outstanding member of this group is caffein, which in the form of coffee is, apart from carbon dioxide, the most valuable of respiratory stimulants. It increases the rate and depth of breathing, probably through the augmented tonus and metabolism of the musculature of the body. This stimulation is most marked in the first 10 and 15 minutes, but wears off in the course of a few hours, and may be followed by lassitude.

A more prolonged effect is induced by strychnine. A generation or more ago, when it was customary to prescribe a tonic for all patients who were "run down," strychnine more commonly than any other medicine was prescribed in various mixtures to be taken "three times daily" after meals. Strychnine was then regarded as a heart stimulant. Modern pharmacology, however, has demonstrated conclusively that strychnine has no such direct action on the heart; and that its chief effects are the accentuation of the spinal reflexes, and the consequent increase of muscle tonus. Yet indirectly this effect is sufficient to augment both the heart action and respiration. The tonus of the muscles is a major factor in the heat production, oxygen consumption and carbon dioxide production of the body. The amount of carbon dioxide produced determines the volume of respiration; and the tonus of the muscles induces also that pressure throughout the tissues of the body which to a large extent determines the volume of the venous return to the heart, and the volume of the circulation.

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De Universitate nihil
Nisi bonum; ergo nihil.

