ACAPNIA AND SHOCK. — I. CARBON-DIOXID AS A FACTOR IN THE REGULATION OF THE HEART-RATE.

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[From the Physiological Laboratory of the Yale Medical School.]

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ORIGIN OF THE PROBLEMS.

In major surgical operations a pulse of extreme rapidity and correspondingly small amplitude is a dangerous symptom. Indeed a progressive increase in heart-rate up to extreme tachycardia is one of the features in the development of at least one form of shock. Yet the surgeon is often practically helpless when confronting such a progressively rising pulse, since he cannot intelligently counteract a process if he is ignorant of its cause. In the course of a series of experiments involving extensive operative procedures upon dogs we experienced a large number of failures.

1 Preliminary reports upon various parts of this subject were presented by the writer before the Physiological Section of the British Medical Association in August, 1906 (published in the British medical journal, 1906, ii, p. 1812), and before the American Physiological Society in December, 1905, December, 1906, and May, 1907 (This journal, 1906, xv, p. xviii; 1907, xviii, p. xv; and 1907, xix, p. xiv). Portions of the subject matter of this paper were presented in the theses for the M.D. degree by F. P. CHILLINGWORTH and J. R. COFFEY, to the Faculty of the Yale Medical School, June, 1907.
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Tachycardia and then shock developed. As this result seemed to us inexplicable by any principles of physiological reaction at present recognized, we were stimulated to discover, if possible, its hidden cause.

It is well known that healthy dogs are with difficulty brought into a condition of shock. Violent procedures, such as cauterization of a large area of the peritoneum,\(^2\) crushing of a limb, and other forms of intense and prolonged stimulation of many afferent nerves, have generally been found necessary to induce this condition. Even under such treatment a dog which has received a dose of morphine and is maintained under moderate anesthesia will not infrequently survive for many hours. The primary purpose of the series of experiments, among which occurred the failures to be here analyzed, was the study of the normal activity of the dog's heart under conditions as nearly physiological as possible. The utmost care was exercised therefore to avoid such injuries and stimulations. Yet during our earlier experiments we repeatedly saw the animals die in shock after passing through all the typical stages of this condition within two hours after the beginning of the experiment, and occasionally even within a much briefer period. These cases were the more enigmatic because other animals, which had received a precisely similar treatment, — so far as we were then aware, — maintained for many hours the normal slow heart-rate and high blood pressure requisite for the observations which were the primary object of the experiments.

Before the completion of this series of experiments these difficulties had been so far overcome that we could at will induce or prevent the occurrence of shock. Moreover the method employed to this end proved to be highly effective also as a means of varying the heart-rate. By this method we were enabled to regulate the heart to any desired rate from 40 or fewer up to 200 or more beats per minute. The method was very simple. It depended on the manipulation of the hand bellows with which artificial respiration was administered and on the adjustment of the escape vent in the side of the cannula tied into the trachea. As the pulmonary ventilation was increased or diminished the heart rate was correspondingly accelerated or retarded. This method was utilized successfully on a large number of dogs, in which the behavior of the heart at various rates of beat was recorded. Since the results

\(^2\) Cf. T. Sollmann: This journal, 1907, xx, p. 74.
thus obtained were published,\textsuperscript{3} our attention has been devoted to investigations on the causal relations between the method and its results. The scope of these investigations has widened until they cover a great part of the entire subject of surgical shock and touch on a number of related topics. They will require a series of papers for detailed presentation. The hypothesis to the demonstration of which the entire series will be directed is as follows:

\textbf{Acapnia as the Cause of Surgical Shock.}

From the data to be presented in this series of papers it appears that the CO\textsubscript{2} content of the blood exercises regulative influences upon the heart-rate, upon vascular tonus, upon the peristalsis of the alimentary canal, upon the mental condition and upon a number of other functions of the body to a degree, so far as we can find from the literature, hitherto in great part not demonstrated. These data show that even a slight reduction in the CO\textsubscript{2} content of the arterial blood causes a marked quickening of the heart-rate. Further reduction induces an extreme tachycardia, complete cessation of peristalsis, failure of many reflexes, and coma. If an extreme reduction of the CO\textsubscript{2} content of the blood is effected very rapidly the heart comes into a state bordering on tetanus. This cardiac tetanus practically abolishes the pumping action of the heart. Arterial pressure falls therefore; and death results.

If the reduction in the arterial CO\textsubscript{2} is less extreme but is maintained for a considerable time (an hour or more according to the extent of the reduction), so that the tension of CO\textsubscript{2} in the venous blood and in the tissues is greatly reduced, symptoms and conditions result which are similar in many respects to those occurring in mountain-sickness, and are apparently identical with those of surgical shock. Arterial pressure falls to a very low level; and if the condition is continued the circulation fails. This fall is not due merely to tachycardia, for the heart-rate in the later stages is not always extremely rapid, but is caused by a loss of tonus in the peripheral veins and capillaries, and by the consequent stagnation of the blood in these vessels. The mental condition of the subject is comatose. The reflexes are greatly reduced in responsiveness. Vigorous stimulation of afferent nerves causes no rise of

\textsuperscript{3} \textit{Y. Henderson:} This journal, 1906, xvi, p. 325.
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arterial pressure. This condition of the nervous system and the stage of excitement through which it develops, are not due primarily to the fall of arterial pressure. They precede the fall. Although the coma is of course intensified by a low pressure, it may occur to a considerable extent coincidently with the high pressure of the earlier stages.

The respiration, when the subject is left to breathe naturally, becomes very shallow. It is liable to pass into apnoea. This condition is the direct effect of the reduced CO₂ tension in the respiratory centre.

The reduction of CO₂ leading to these conditions can be effected by excessive artificial respiration. It can be effected by allowing the subject, after the thorax has been opened, to breathe by the Sauerbruch-Brauer method an excess of fresh compressed air. To a certain extent the conditions above described can be induced by a normal man upon himself by voluntarily forced respiration. They result to a considerable extent from the hyperpnoea incident to the stage of excitement of incomplete anaesthesia. The hyperpnoea induced by vigorous and prolonged stimulation of afferent nerves—a condition which, in an animal or man not anaesthetized, would be one of extreme pain—is an effective procedure for the reduction of the CO₂ content in the blood. Morphine and complete anaesthesia counteract the development of shock by quieting the respiration. Diminution of the dead-space of the respiratory tract by tracheotomy removes an important natural check on excessive pulmonary ventilation. The expression "excessive" in this and similar connections is used to indicate the maintenance of a sub-normal tension of CO₂ in the alveolar air.

Exposure of the abdominal viscera to the air so as to allow a free exhalation of CO₂ from the surface of these organs induces, even when no further operation is performed, and when both cooling and drying are prevented, an extreme congestion in the part exposed. This congestion is relieved by placing the part in saline saturated with CO₂. If a general abdominal congestion has been thus induced and is then followed by even a moderate hyperpnoea through the stimulation of an afferent nerve, the subject passes within a few minutes into shock.

In the production of these conditions variations in the oxygen content of the blood appear to play little, if any, part. Artificial regulation of the heart-rate by the method which we have employed
appears to depend upon the regulation of the CO₂ tension of the air in the pulmonary alveoli, and thus upon the extent to which CO₂ is ventilated out of the blood in its passage through the lungs. The condition of shock which results in man from extreme physical suffering is to a large extent, we believe, caused by the reduction of the CO₂ content of the blood and tissues below the normal tension by the violent and prolonged hyperpnoea induced by the stimulation of afferent nerves. The peculiar liability of laparotomy to result in shock is, we believe, due to the exhalation of CO₂ from the parts exposed. Out of a very large number of experiments involving extensive and prolonged operations the symptoms of shock as above described have never developed in a single case in which any considerable loss of CO₂ below the normal was prevented.

In a number of experiments in which shock had been induced, restoration of CO₂ to the tissues and blood (or rather the maintenance of a condition which permits the tissues rapidly to restore their CO₂) proved effective in inducing a rapid recovery. Consciousness and the normal reflexes returned simultaneously. The intestines recovered their automatic motility. Such a restoration is most easily accomplished by infusing saline saturated with CO₂, and simultaneously increasing the dead-space of the respiratory tract by causing the subject to breathe through a tube of about double the diameter of the trachea and 50 to 100 centimetres’ length. Under all conditions, except during hyperpnoea, in which condition the cardiac activity is increased sympathetically with the respiratory excitement, and to a certain extent even in this condition, the heart-rate can be kept down and the development of shock prevented by the use of such a tube. In the absence of respiratory excitement the heart-rate is an index which varies inversely as the CO₂ content of the arterial blood.

Carbon-Dioxxid as a Hormone.

In discussing the subject of the “Chemical Co-ordination of the Functions of the Body” in the “Ergebnisse der Physiologie,” Bayliss and Starling have given the first place to carbon-dioxxid as the “hormone” or chemical regulator of respiration.4 From

the extensive literature of respiration and from the more meagre
and less definitely determined knowledge regarding the influence
of CO₂ in regulating other functions of the body we shall here cite
only such points as appear to bear directly on the conclusions stated
in the preceding section.

The observations of Haldane and Priestley⁵ have afforded cru-
cial evidence that "the regulation of the rate of alveolar ventila-
tion in breathing depends, under normal conditions, exclusively on
the CO₂ pressure in the respiratory centre." In their experiments
normal men were subjected to a wide variety of conditions in re-
spect to the oxygen tension in the air breathed, — variations up
to a full atmosphere of oxygen and down to only 13 per cent of
an atmosphere partial pressure of this gas, — without the respira-
tory movements showing any reaction to these variations, and
without the subjects themselves perceiving any alteration in their
own condition. On the other hand, when the subjects were exposed
to a wide variety of conditions in respect to barometric pressure
and to the CO₂ content of the air breathed, the respiration was found
to vary in such perfect adjustment to these conditions that the
tension of CO₂ in the alveolar air was maintained nearly constant.
Not only is the respiratory centre exquisitely sensitive to any rise
in CO₂ pressure, — a rise of 0.2 per cent of an atmosphere in the
alveolar air being, for instance, sufficient to double the amount
of the alveolar ventilation during rest, — but the respiratory centre
is almost equally sensitive to even a slight reduction in the tension
of CO₂ below the normal (about 5.5 per cent of an atmosphere).
Thus a brief period of voluntarily forced respiration in man is
followed automatically by an interval of apnoea. As evidence that
this apnoeic pause is due to the temporary lowering of the CO₂
tension of the arterial blood below the threshold exciting value for
the respiratory centre, Haldane and Priestley find that in man it
does not occur when the air forcibly respired contains CO₂ of nearly
the same tension as that of the alveolar air.

It has long been known that vigorous artificial respiration is
followed by a period of apnoea. In a review of the earlier inves-
tigations on this subject Miescher⁶ pointed out that this pause
might consist of two conditions, which he termed respectively

⁵ Haldane and Priestley: Journal of physiology, 1905, xxxii, p. 225. See
also Fitzgerald and Haldane: Journal of physiology, 1905, xxxii, p. 486.
apnoea spuria and apnoea vera. The former is the result of the stimulation of the afferent nerve endings of the vagi in the lungs, by which the respiratory centre is temporarily inhibited. The latter is the effect upon this centre of the blood which is over-aerated by the excessive pulmonary ventilation. The changes in the blood might consist in an over-oxygenation or in a reduction of its content of CO₂. The first of these alternatives is rendered untenable by the fact that apnoea is not induced, indeed the rate and depth of respiration remain unaltered, when the subject breathes pure oxygen. In this case the alveolar tension of oxygen is increased far above the maximum attainable when the lungs are ventilated merely with air,—no matter how rapid the ventilation. Thus, as Miescher concluded, and as the recent investigations of Fredericq,⁷ of Mosso,⁸ of Weil,⁹ and of Haldane and Priestley¹⁰ have verified, apnoea vera is caused by the diminution in the CO₂ of the arterial blood.

This conclusion as to the much disputed causation of apnoea is important in connection with the matters to be discussed in the present paper, because we have employed as the means of inducing tachycardia and shock the same procedures as those which induce apnoea vera. The facts and reasoning which have led previous writers to this explanation of apnoea vera may therefore be adduced with equal validity in support of the view that tachycardia and the other conditions which result from excessive pulmonary ventilation are also due to diminution of CO₂. For the solution of the problem of surgical shock this explanation of apnoea is of fundamental importance. In the extensive investigations on surgical shock performed by Crile,¹¹ it was found that in 90 per cent of the subjects death was due to respiratory failure. "In many instances the heart was beating strongly and blood pressure was fair at the time respiration failed." These observations alone would go far to show that diminution of CO₂ is a factor in surgical shock, were it not for the fact that the literature of respiration presents with the weight of many authorities two other explanations of the regulation of respiration and the causation of apnoea.

⁷ Fredericq: Archives de biologie, 1901, xvii, p. 563.
⁸ Mosso: Archives italiennes de biologie, 1903, xl, pp. 19 et seq.
¹⁰ Haldane and Priestley: Loc. cit.
¹¹ Crile: Surgical shock, 1899, p. 143.
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One of these explanations is that respiration is essentially a reflex function, and that the discharges from the respiratory centre are the reaction to the augmentor and inhibitory influences of afferent nerves, and especially of the pulmonary fibres of the vagi. The standing of this explanation at the present day is estimated by Boruttau, in the statement that the last supporter of “the purely reflex nature of the respiratory movements has taken his views to the grave with himself.” It is reasonable, therefore, to reject the idea that the shallow respiration consequent on vigorous and prolonged artificial respiration is due to a lasting inhibition of the respiratory centre by stimulation through the vagi. It is reasonable also to reject the idea that the failure of respiration in shock following the hyperpnoea of pain indicates exhaustion of the respiratory centres by the stimulation of afferent nerves. Finally, by the same logic applied to closely similar facts, it is reasonable to reject the idea that the disturbances of the circulation in shock are the expression of the state into which the vaso-motor centre is thrown by the stimuli reaching it through afferent channels. Porter has in fact presented data which are opposed to the hypothesis that surgical shock is an exhaustion of this centre. Yet this hypothesis, supported by Crile, is generally accepted at the present time.

A third explanation of the causation of the variations in respiratory, cardio-regulative, vaso-motor and other functions has behind it a greater weight of authority, although, as we believe, a much smaller amount of evidence, if interpreted in its true significance, than either of the explanations above quoted. Because oxygen is a vital necessity, and CO₂ only a waste product, it has appeared natural to many writers to infer that the oxygen tension of the blood must exert profound and extensive regulative influences.

12 H. Boruttau: Ergebnisse der Physiologie, 1904, Dritter Jahrgang, ii Abteilung, p. 95. For reviews of other phases of this subject, see E. H. Starling, Nervous mechanism of respiration, Schäfer’s Textbook of physiology, 1900, ii, p. 283; R. Magnus: Pharmakologie der Atemmechanik, Ergebnisse der Physiologie, 1903, Erste Jahrgang, ii Abteilung, p. 414; R. du Bois-Reymond, Mechanik der Atmung, same volume, p. 378; C. Bohr, Blugase und respiratorischer Gaswechsel, Nagel’s Handbuch der Physiologie des Menschen, 1905, i, p. 54; L. Frederico, on Apnoea, and Richet on Asphyxia, Dictionnaire de physiologie par Charles Richet, 1895, i, pp. 630 and 728.

13 W. T. Porter: This journal, 1907, xx, pp. 399 and 500.

14 Crile: Keen’s Surgery, 1906, i, p. 922.
Rosenthal and his followers attempted to explain apnoea and hyperpnoea on the ground respectively of excess and of deficiency of oxygen. Because a flame burns the brighter the richer the atmosphere is in oxygen, it appears natural to infer that the vital combustions of the body must be increased in vigor by an increase in the supply of oxygen to the lungs. That such is not the case, however, but that the rate of oxygen consumption by the animal body is independent of an excess in the supply was proved conclusively by Pflüger more than thirty years ago, and has since been verified by many investigators.

In the recent literature the discussion of this subject has turned largely on the extensive investigations of the phenomena and causes of mountain-sickness. Throughout the literature of this disorder, excepting only in the writings of Mosso and his adherents, its symptoms have been undoubtingly explained as due to lack of oxygen. The liberal use of oxygen in clinical medicine indicates the current opinion on this subject among physicians. Surgeons profess their faith that lack of oxygen occurs and is a cause of diminished functional activity by administering this gas to cases in shock.

Kraus in an exhaustive review of the clinical literature of this subject has expressed an opinion adverse to the value of oxygentherapy.

Durig (loc. cit. p. 363) makes the pregnant suggestion that the beneficial effects of oxygen inhalation are in great part due to the considerable quantity of CO₂ which the oxygen employed in the clinic usually contains. We would also call attention to the fact that the mask by which the gas is administered increases the dead-space of the respiratory tract, and thus causes the patient to some extent to re-breath his expired air.

For a refutation of Rosenthal's argument see the paper (from the laboratory of Zuntz) by A. Durig: Archiv für Physiologie, 1903, Supplement, p. 209.

Pflüger: Archiv für die gesammte Physiologie, i, pp. 61, 274, and 686; ii, p. 136; x, p. 251; xiv, p. 1; xix, p. 244. See also Voit: Zeitschrift für Biologie, 1907, xli, p. 1.

For reviews of this literature, see O. Cohnheim, Physiologie des Alpinismus, Ergebnisse der Physiologie, 1903, ii, p. 612; Zuntz, Löwy, Müller, and Caspari; Hohenklima und Bergwanderungen, 1906, chapters xi, xii, xviii, and xix; and Recent advances in physiology and bio-chemistry, 1906, edited by Hill, chapters viii and xy.

Kraus: Zeitschrift für klinische Medicin, xxii, p. 449.
Among physiologists the vaso-constriction and slow heart-rate of asphyxia have generally been regarded as the effects of lack of oxygen. Verworn in particular reached the conclusion that lack of oxygen is the primary cause of the vagus pulse in dyspnoea, and that in this respect the increase of CO₂ in the blood is of very minor, if of any, significance. He supported this conclusion by the statement, which if it were correct would prove his conclusions, that "from the investigations of Rosenthal and others it is to-day well established that lack of oxygen is the primary stimulus to the respiratory centre in dyspnoea, while the increased CO₂ as an exciting influence is of very secondary importance." It appears to us on the contrary that the literature bearing on the question affords overwhelming evidence that oxygen, not merely in respect to these functions but also in its general relations to protoplasmic activity, exerts a relatively low potency as a hormone.

Recent investigations have tended to show that the excitement of the vaso-motor centre in asphyxia is caused rather by the excess of CO₂ in the blood than by lack of oxygen. Thus the effects of a subnormal pulmonary ventilation and the consequent venous condition of the arterial blood upon the respiratory, cardio-regulative, and vaso-motor centres are all principally due to the increase of CO₂ rather than to diminution of oxygen. It is probable that many symptoms which physicians have regarded as due to lack of oxygen are really caused by alterations in the conditions and mechanism on which the maintenance of the normal tensions and contents of CO₂ in the blood, tissues, and nerve centres depend. For the needs of the body in respect to oxygen the regulation of respiration by CO₂ maintains a broad margin of safety.

On the effects of a reduction of the CO₂ tension of the blood below the normal, the most important contributions have been made by Mosso and his co-workers. In a large number of papers they have presented evidence to show that under reduced barometric pressure the CO₂ content of the blood is diminished, and that this

19 For a review of the literature bearing on this and related questions, see R. TIGERSTEDT: Ergebnisse der Physiologie, 1903, ii, 2, pp. 567-571.
20 M. VERWORN: Archiv für Physiologie, 1903, p. 65. For the views of VERWORN on the relations of oxygen and of CO₂ to nervous activity on his "Biogen-Hypothesis," see Archiv für Physiologie, 1900, Supplement, p. 152.
diminution is one of the causes of the disturbances of function in mountain sickness. For this condition Mosso has suggested the convenient term “acapnia” (from ΚΑΠΝΩΣ, smoke, — literally smokelessness). Mosso and Marro have shown by blood-gas analyses that when animals are transported up to the physiological laboratory on Monte Rosa or are placed in the low pressure chamber in the laboratory in Turin, the CO₂ content of the arterial blood is reduced. In experiments on monkeys in this chamber, even when pure oxygen was supplied in such quantities as to eliminate the possibility of lack of oxygen playing any part in the reactions, a lowering of the barometric pressure induced muscular weakness, sleepiness, and at times almost vomiting. The observations of Mosso and of Aggazzotti on men, monkeys, dogs, and rabbits show that under reduced barometric pressure, when the subject is at rest, respiration is markedly diminished in amplitude while accelerated in rate. These observations may be taken on the one hand as indicating the reaction of the respiratory centre to the lower tension of CO₂, and on the other as an adjustment which tends to prevent its further loss.

Considering the large number of investigators who have studied the production of apnoea by excessive artificial respiration, it is surprising that the fact is not today well established that acapnia immediately produces tachycardia and, if long continued, always results in shock. We certainly are not the first to observe the production of shock in this way. Thirty-four years ago Ewald, working in Pflüger’s laboratory, noted that the arterial pressure of a dog which for twenty minutes was subjected to vigorous artificial respiration fell from 154 to 65 mm. of mercury. The fall was due to a very great diminution in the output of the heart, — down to 25 or 30 per cent of that during normal respiration. Pflüger showed at the same time that the oxygen consumption of the body was not altered by the ventilation. Ewald’s analyses showed that the oxygen content of the arterial blood, if altered at all, was slightly increased. The oxygen content of the venous

28 Mosso and Marro: Archives italiennes de biologie, 1903, xxv, pp. 387, 395, and 402; also 1904, xli, p. 337.
29 Mosso: Archives italiennes de biologie, 1904, xli, pp. 384 and 397; also 1904, xlii, p. 23; also 1905, xliii, pp. 81, 209, 341, 355, and 467.
30 A. Aggazzotti: Archives italiennes de biologie, 1904, xlii, pp. 14, 43, and 53; also 1905, xlii, pp. 39, 137, 150, and 343.
blood was greatly diminished. In one experiment, after thirty-five minutes' ventilation, the oxygen content of the venous blood had fallen from 11.7 to 4.6 volumes per cent. The oxygen content of simultaneous samples of arterial blood was 17.3 and 17.9. The cause of the diminution in the blood stream thus indicated lay, as Ewald concluded, either in an alteration of the innervation of the blood vessels and heart, or in a venous congestion (due to the increase of resistance in the lungs by the ventilation), or in both conditions. In the experiment from which these analyses are quoted the extent of the arterial acapnia is shown by the fact that the CO₂ content fell from 33.4 to 17.5. The venous acapnia in this case was relatively slight, — the figures showing 36.5 volumes per cent of CO₂ before and 33.9 after thirty-five minutes' ventilation. In other experiments figures as low as 15 to 18 per cent CO₂ in the venous blood were repeatedly obtained after ventilations of an hour or more. Since the tensions of the gases in the venous blood must be very nearly the same as the tensions in the tissues from which the blood flows, — just as the tensions in the arterial blood are nearly the same as those in the alveolar air of the lungs, — a very considerable washing out of CO₂ from the tissues as the result of the ventilation is indicated by these figures.

In experiments similar to those of Ewald, Mosso has likewise noted acapnia, apnoea, tachycardia, and fall of arterial pressure. He has also observed in man a lowering of blood pressure and quickening of the heart-rate coincident with the apnoea produced by forced respiration. As regards the effects of acapnia upon the circulation, the observations of Ewald, of Mosso, and of ourselves are in these respects identical. Neither Ewald nor Mosso has, so far as we can find, suggested that the condition induced by extreme acapnia is that of surgical shock. Nor, so far as we can discover, has any one prior to ourselves shown that after the opening of the thorax the heart-rate is completely controllable by regulation of the CO₂ content of the blood.

Many writers have commented upon the similarity of surgical shock and mountain-sickness. Wetherill and Powers have observed that in Denver (altitude 5260 feet) persons who have

recently come from sea-level are in surgical operations peculiarly liable to shock.

Comparing the condition of the nervous system in shock with the condition induced by experimental acapnia, we find striking similarities. Rosenthal recognized that many of the nerve centres are brought into a condition of diminished tonus and diminished irritability by the alteration in the blood gases during and after excessive artificial respiration. Kronecker and Markwald found that under such circumstances the respiratory centre is irresponsible to direct electrical stimulation. Leube found that in rabbits which had received a dose of strychnine sufficient to kill under ordinary conditions convulsions were prevented, and the animals recovered when a somewhat excessive rate of artificial respiration was maintained. Paul Bert noted that in rapid balloon ascensions there occurred first a period of mental excitement, followed by a period of somnolence, exhaustion and disturbances of sight and hearing. Aggazzotti has shown on men and animals that lowered barometric pressure diminishes reflex irritability, the acuteness of hearing, and probably that of the other senses also. He likewise observed muscular weakness. Conversely Lee has recently shown that the increase of functional activity expressed in the phenomenon of the Treppe occurs in the muscles of mammals when the tension of CO2 in the blood and tissues is increased by asphyxia.

Similar relations between the tension of CO2 in the tissues and their functional activity are observable in respect to the motility of the alimentary canal. It is well known that mere opening of the abdomen abolishes the peristalsis of the stomach and greatly reduces that of the intestines. Nor is motility completely restored for a considerable period after the abdomen is reclosed. The stand-
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still is not due to drying, for it occurs in a bath of saline, as shown by the observations of Johannes Müller, of Pal, and recently of Auer.\textsuperscript{36} On the contrary, if the trachea be occluded the exposed intestines exhibit for a brief period vigorous peristalsis. Strangely enough it appears to have occurred to no one to inquire whether (as we find to be the case) the exhalation of CO$_2$ from the moist peritoneum and the hyperpnoea induced by the operation are the causes of the cessation of peristalsis after laparotomy.

The human skin is very slightly pervious to CO$_2$.\textsuperscript{37} So long as the skin is unbroken and there is no sensible perspiration, the tissues are protected from loss of CO$_2$ except by way of the circulation. The minimum tension of CO$_2$ in any tissue can never be less than its tension in the arterial blood. This tension in turn is determined by the partial pressure of CO$_2$ in the alveolar air of the lungs. It is accordingly interesting to note that the respiratory tract of all the higher animals includes a large dead-space,—having in man a volume equal to 30 per cent of an ordinary inspiration,—which can scarcely be regarded as useful in respect to the oxygen supply of the body, but is an important factor in the maintenance of the normal high tension (5.5 per cent of an atmosphere) of CO$_2$ in the alveolar air. Paul Bert\textsuperscript{38} found that the CO$_2$ content of the arterial blood was diminished after tracheotomy. Thus:

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<td>Before tracheotomy</td>
<td>15.1</td>
<td>40.8</td>
<td>16.0</td>
<td>41.5</td>
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<td>After tracheotomy</td>
<td>20.3</td>
<td>24.0</td>
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If the CO$_2$ content of the blood supplied to the nervous system exerts under the normal conditions of life regulative influences of the potency which our investigations indicate, it would appear that could an individual acquire the ability voluntarily to increase or diminish the rate of pulmonary ventilation marked alterations in the condition of the nervous system might be expected to result. In fact breathing exercises have in recent years been successfully employed as part of the treatment for neurasthenia in some sanitarium. Among a number of the semi-religious, semi-philosophical cults and sects which have gained adherents in America in recent

\textsuperscript{36} \textit{Auer}: This journal, 1907, xviii, p. 347

\textsuperscript{37} \textit{Schierbeck}: Archiv für Physiologie, 1893, p. 123.

\textsuperscript{38} \textit{P. Bert}: La Pression barometrique.
years, and which have in one form or another held up as the chief object of their practices the attainment and maintenance of physical health and the control of the vegetative functions of the body by the mind, breathing exercises have been extensively developed. Noteworthy are the elaborate breathing exercises of the Yoga or Vedanta Philosophy.\footnote{For an interesting account of these practices and their results, see the article by Professor WM. James, Science, 1907, xxv, pp. 326-328.} For more than two thousand years these exercises have been practiced in India as the means through which, as claimed, the subject can gain control over the heart-rate and other functions, can render himself insensitive to pain, or even unconscious, and can induce mental exaltation and hallucinations. In some of the older works on surgery it was directed that prior to a minor operation the subject should for a few minutes perform forced respiration. The relations of pain to respiration, and of respiration to pain, are as yet little understood.

Finally the question arises, Do variations in the CO₂ content of the arterial blood play any considerable part in conditioning the variations in the heart-rate which in a normal man occur with every bodily movement, with every change of position, and with every emotion? The investigations of Haldane and Priestley already quoted make it altogether probable that under nearly all normal conditions the variations in the CO₂ tension in the arterial blood are very slight. The threshold exciting value of the respiratory centre in respect both to increase and to diminution in the tension of CO₂ is so low in comparison with the other centres, such as the cardio inhibitory, that the above question can be answered quite clearly in the negative. Hypo- and hyper-capnia are abnormal conditions. Moreover, the investigations of Fredericq\footnote{FREDERICQ: Archives de biologie, 1882, iii, p. 75. For the extensive literature of this subject, see TIGERSTEDT, Lehrbuch des Kreislaufs, 1893, p. 453; also TIGERSTEDT, Ergebnisse der Physiologie, loc. cit.} on the relations of the heart-rate to the activity of the respiratory centre have demonstrated the intimate sympathy between this centre and those controlling the heart-rate. Thus respiratory excitement (or indeed excitement in any part of the nervous system) always exerts a cardio-accelerative influence. Voluntary holding of the breath by a man, or breathing through a large dead-space, or asphyxiation on an animal causes primarily not a slowing but an acceleration of the heart-rate because of the respiratory excitement. The in-
stant this respiratory excitement ceases the heart rate becomes extremely slow because (as the work of Verworn and others has shown) of the asphyxial condition of the blood. Vagus-tonus is generally regarded as the principal factor in determining the heart-rate. It appears therefore that an asphyxial (or hypercapnial) condition of the blood supply to the spinal bulb exerts a stimulating influence upon both the respiratory and the cardio-inhibitory centres. Experiments of Mosso, in which the heart-rate even after vagus section was accelerated by excessive artificial respiration, make it probable also that acapnia stimulates or that CO₂ exerts an inhibiting influence upon the cardio-accelerator mechanism.

Although variations in the CO₂ content of the blood are therefore not factors in the momentarily occurring normal variations in the heart-rate, the heart-rate of every individual when at rest is, we believe, principally determined by the CO₂ content of the blood. Slight alterations in the sensitivity of the respiratory centres and the consequent alterations in the tension of CO₂ in the blood would afford a sufficient cause for the variations in the pulse rate which occur in many abnormal conditions.

Hypo-capnia has in fact been found to occur in many forms of fever both in men and animals, in diabetic coma, in the condition consequent on violent muscular exercise, and in that form of shock which results from the intravenous injection of albumose or "peptone." In all of these conditions, as well as in mountain-sickness, excessive artificial respiration, and surgical shock, there occur at one stage or another and in varying order hyperpnoea, followed by shallow respiration or apnoea, tachycardia, venous congestion and fall of arterial pressure, muscular weakness, suppression of reflexes, disturbances of consciousness, and disturbances of the motor functions of the alimentary canal.

VERWORN: Loc. cit.

For literature, see F. B. HOFMANN, in NAGEL'S Handbuch der Physiologie des Menschen, 1905, i, Erste Hälftte, p. 276.

Mosso: Archives italiennes de biologie, 1904, xli, p. 200.

For a review and bibliography of this subject, see L. KREHL, Pathologische Physiologie, third edition, 1904, pp. 459 and 475.

BEDDARD, PEMBREY, and SPRIGGS, Journal of physiology, 1904, xxxi, p. xlv.

HILL and FLACK, Journal of physiology, 1907, xxxvi, p. xi.

LAHOUSSE: Archiv für Physiologie, 1889, p. 77.
The object for which our earlier experiments were planned was to record the volume curve of the ventricles of the heart. Twenty-five dogs were used.

The animals received subcutaneously a moderate dose of morphine and were then anesthetized with ether. The thorax was opened by an incision directly down through the skin and through all of the costal cartilages at their junctions with the ribs, so that the sternum and costal cartilages with their adherent musculature and skin formed a lid hinging upon the clavicles. A single ligature was then placed about the internal mammary arteries and veins near the origin of the arteries. In none of the experiments to be discussed in this paper was there any considerable hemorrhage. The pericardial sack was opened and rolled back from the heart. A cardiometer (described in the previous paper already referred to) was slipped on over the ventricles so that their volume changes were recorded by a large tambour connected with the interior of the cardiometer by a rubber tube. Blood pressure was recorded by a Hürthle manometer connected either with the carotid or with a sound inserted into the left ventricle.

Owing to the fact that the apparatus for artificial respiration happened at the time to be out of order, air was supplied to the lungs by means of a large hand bellows connected directly with a cannula tied into the trachea. The animals were thus subjected to a ventilation which, as later experiments have shown, was in excess of their needs. We were at that time unaware of the evil effects of excessive pulmonary ventilation. When it was seen that the blood pressure was falling in spite of (or because of) a tremendous heart-rate, we supposed that the respiration must be insufficient. Accordingly the escape vent of the tracheal cannula was opened wide, and the lungs were filled as fully and at as rapid a rate as possible. In fact the arrangement of the respiration apparatus was such as not only to fill the lungs to their maximum capacity with each down-stroke of the bellows, but also to exert with each up-stroke a slight suction on the lungs, and thus to accelerate their collapse. The alveolar air must thus have been kept nearly at the same composition as that of the laboratory, while normally it contains some 5 or 6 per cent of CO₂.

For the literature bearing on this subject and for an experimental demonstration that the mammalian heart is capable of tetanus, see Danilewsky, Archiv für die gesammte Physiologie, 1905, cix, p. 596.
Acapnia and Shock.

Under such treatment it twice happened that the subject of the experiment was dead within half an hour after the thorax had been opened and artificial respiration begun. The cause of death was the cessation of the pumping action of the heart. The ventricles became so contracted, because of the great rapidity of beat and extreme Treppe, that the ventricular chambers were almost obliterated. Immediately after death the cardiometer was removed, and it was found that although the auricles were still beating, the ventricles were hard and incompressible. To the eye and finger the muscle appeared to be in a complete tetanus. A few minutes later the right ventricle relaxed and was responsive to mechanical stimulation.

Since the thorax was open it is improbable that mechanical obstruction to the pulmonary circulation played any considerable part in the results. Doubts on this point are further negatived by the results of later experiments.

Acapnia under Artificial Respiration.

In those experiments in which the artificial respiration was administered less vigorously, although still in excess, the progress of events was much less rapid. Tachycardia developed to a degree sufficient to cause a marked but not an immediately fatal fall of arterial pressure. The animals then passed into a condition of shock; and death, which in these cases occurred in from one to three hours after the opening of the thorax, was due not to cardiac tetanus, but to failure of vascular tonus. Indeed, in later experiments it was found very difficult to induce cardiac failure through extreme tachycardia except in small animals, in which the thorax was widely opened and the pulmonary ventilation extremely rapid.

In the larger animals there developed quite uniformly a stage in which the up-strokes of the volume curve of the heart (indicating the rate of filling of the ventricles during diastole) were much less abrupt than when the animals were fresh. This retardation of the diastolic filling was especially noticeable at intervals when, coincident with a less vigorous working of the bellows, the rapidity of the heart-rate was reduced. At such times the heart did not recover the amplitude of beat normal for the slower rate. The volume of blood pumped out into the arterial system by the heart was therefore greatly reduced. The alteration in the form of the
volume curve was similar to that exhibited by a striated muscle in
the slow relaxations of the early stages of fatigue. This similarity,
however, was only superficial. The heart was not fatigued. When
saline was infused into a vein the abruptness of the up-strokes of
the volume-curve immediately reappeared. During the time that
the beneficial effects of the infusion lasted the normal amplitude
of beat was regained, and arterial pressure was restored to a normal
or nearly normal level. These observations indicated clearly that,
as one of the results of excessive pulmonary ventilation, the tonus
of the venous system was reduced to a point at which a stasis of
the blood in the veins occurred. Thus the venous supply to the
right heart was reduced. Finally the venous supply failed almost
completely; the pumping action of the heart was abolished; and
the arterial circulation ceased.

The conditions observed in these experiments appear to be iden-
tical with those which clinical and experimental observations have
established as the cause of the failure of the circulation in surgical
shock.\(^9\) As regards the state of the respiratory centre, a pro-
longed apnoeic pause was noted invariably when the artificial res-
piration was suddenly discontinued in the earlier stages. In the
later stages we have repeatedly seen the apnoeic pause prolonged
until the heart ceased to beat (probably from lack of oxygen), with-
out the slightest respiratory effort on the part of the animal.
Equally marked were the effects of the excessive pulmonary venti-
lation upon other centres in the nervous system. The animals were
usually only partially morphinized. Under moderate artificial res-
piration a constant administration of anaesthetic (usually ether)
was necessary. Under excessive artificial respiration they usually
appeared almost completely comatose. In this condition no anaes-
thetic was needed. This was the case even during the earlier stages,
while arterial pressure was at a normal level or even above the
normal. Even in the earlier stages vigorous stimulation of an
afferent nerve (pinching, or electrical stimulation of the sciatic
nerve, burning the foot, etc.) often failed to elicit a rise of arterial
pressure. In the later stages such stimulations were invariably

\(^9\) CRILE: An experimental research into surgical shock, 1899; CRILE: Blood
pressure in surgery, 1903; HOWELL: Contributions to medical research dedicated
to V. C. VAUGHAN, 1903, p. 51; DAWSON: Journal of experimental medicine,
1905, vii, p. 1. For reviews of the experimental and clinical literature, see MOM-
MERY, Lancet, 1905, i, pp. 696, 776, and 846; also CRILE, on Surgical physiology
and on shock and collapse, in KEEF'S Surgery, 1906, i, pp. 79 and 922.
Acapnia and Shock.

wholly ineffective upon arterial pressure, even when sufficiently strong to elicit respiratory movements out of profound apnoea.

With the exception of complete tetanus, all of the variations in the circulation thus far discussed, both the genesis of cardiac tetanus, with its consequent fall of arterial pressure, and the be-

TABLE I.
To accompany Figure 1.

<table>
<thead>
<tr>
<th>Time</th>
<th>Arterial blood gases.</th>
<th>Heart-rate per minute.</th>
<th>Amplitude of beat.</th>
<th>Output of left ventricle per minute.</th>
<th>Arterial pressure.</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O₂ vol. CO₂ per cent.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.30</td>
<td>22.7 37.3</td>
<td>115</td>
<td>..</td>
<td>..</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>12.10</td>
<td>22.7 35.5</td>
<td>130</td>
<td>..</td>
<td>..</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>12.45</td>
<td>6.4    39.1</td>
<td>75</td>
<td>38</td>
<td>1425</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>..     ..</td>
<td>80</td>
<td>23</td>
<td>920</td>
<td>60</td>
<td>Excessive ventilation.</td>
</tr>
<tr>
<td>1.10</td>
<td>..     ..</td>
<td>125</td>
<td>15</td>
<td>937</td>
<td>50</td>
<td>Excessive ventilation.</td>
</tr>
<tr>
<td>1.15</td>
<td>19.1   7.2</td>
<td>230</td>
<td>5</td>
<td>575</td>
<td>60</td>
<td>Excessive ventilation.</td>
</tr>
<tr>
<td>1.25</td>
<td>..     ..</td>
<td>120</td>
<td>9</td>
<td>540</td>
<td>35</td>
<td>Apnoea</td>
</tr>
<tr>
<td>1.50</td>
<td>..     ..</td>
<td>95</td>
<td>8</td>
<td>380</td>
<td>15</td>
<td>Profound shock.</td>
</tr>
<tr>
<td>2.15</td>
<td>..     ..</td>
<td>180</td>
<td>12</td>
<td>1080</td>
<td>40</td>
<td>Saline infusion.</td>
</tr>
<tr>
<td>2.30</td>
<td>..     ..</td>
<td>180</td>
<td>20</td>
<td>1800</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>3.00</td>
<td>..     ..</td>
<td>180</td>
<td>11</td>
<td>990</td>
<td>50</td>
<td>Relapse.</td>
</tr>
<tr>
<td>3.10</td>
<td>..     ..</td>
<td>60</td>
<td>13</td>
<td>390</td>
<td>30</td>
<td>Profound shock.</td>
</tr>
<tr>
<td>3.15</td>
<td>..     ..</td>
<td>50</td>
<td>15</td>
<td>375</td>
<td>20</td>
<td>Profound shock.</td>
</tr>
<tr>
<td>3.30</td>
<td>..     ..</td>
<td>110</td>
<td>7</td>
<td>385</td>
<td>15</td>
<td>Death.</td>
</tr>
</tbody>
</table>

behavior of the heart after loss of vascular tonus, with the consequent diminution in the blood stream, are illustrated in the record (Fig. 1) taken from one of our later experiments. In connection with this experiment the O₂ and CO₂ content of four samples of blood (10 c.c.) drawn from the femoral artery at various rates of heart-beat were determined by means of the blood gas-pump of Leonard Hill. In the table are given the results of these analyses calculated to 0° and 760 mm. of mercury, together with

L. Hill: Journal of physiology, 1895, xvii, p. 353.
Figure 1.—Experiment of July 16, 1906. Dog of 14 kilos. Morphine and ether. Time record in 0.5 second. Arterial pressure recorded from carotid by Hürlle manometer; record graduated in mm. of mercury. Volume curve of ventricles recorded by large tambour connected with plethysmograph on the heart; record graduated in c.c. so that one-half the indicated amplitude of each down-stroke represents the volume of the systolic discharge of the left ventricle. The thorax was opened at 12.15. Excessive artificial respiration was administered for 20 minutes, and the heart-rate was then slowed by lessened artificial respiration until the subject made spontaneous respiratory movements. The cardiometer was placed on the heart (indicated by an arrow) and the first volume curve taken at 12.45. The pulse at this time shows a slight respiratory variation. The artificial respiration was then administered with steadily increasing vigor up to a maximum rate of ventilation at 1.15. The heart-rate increased correspondingly from 80 per minute at 12.45 up to 230 at 1.15. The amplitude of beat diminished correspondingly from 38 c.c. down to 5 c.c. (for both ventricles), and the output of the left ventricle diminished therefore from 1425 c.c. per minute down to 575 c.c. Further increase in the heart-rate to about 300 beats per minute would have brought the heart so nearly into tetanus that its pumping action would have been abolished. Instead of maintaining the excessive ventilation the working of the bellows was diminished at 1.20. The subject passed into shock. At 1.50 the heart-rate was 95, yet owing to the slow filling of the heart in diastole the amplitude was only 8 c.c. and the output per minute of the left ventricle only 380 c.c. Arterial pressure accordingly had fallen to only 15 mm., and the animal was at the point of death. From 2.10 to 2.25 300 c.c. of saline were infused into the femoral vein. The amplitude of the volume curve at 2.30 was thus restored to normal (20 c.c.) for the coincident rate of beat (180 per minute) and the output of the left ventricle rose to 1800 c.c. Arterial pressure was raised thereby to 80 mm. By 3.10 the beneficial effect of the infusion had so far disappeared and the heart was filled so incompletely during diastole that the output of the left ventricle per minute was only 390 c.c. By 3.20 vascular tonus, both arterial and venous was practically abolished. Although so long as artificial respiration was maintained the heart continued to beat feebly, the animal was practically dead at 3.25. See Table I on p. 145.
the heart-rates counted from the pulse curve, and the volume of the blood stream as calculated by multiplying the heart-rate and amplitude of the volume curve, and dividing their product by two, so as to give the output of the left ventricle per minute.

**Artificial Regulation of the Heart-Rate.**

After long uncertainty and many experimental failures, the idea forced itself upon us that in an animal with open thorax, under artificial respiration, and in the absence of any spontaneous respiratory movement, the heart-rate is almost wholly determined by the rate of the pulmonary ventilation. The respiration apparatus shown in Fig. 2 was devised as a simple means of obtaining any

![Figure 2](image_url)

**Figure 2.** In Figure 2 is shown the form of respiration apparatus which, out of several modifications, proved the most convenient for the regulation of the heart-rate. The large hand bellows was fitted with valves both at the inlet and outlet. To the outlet of the bellows was attached air tight a tube 200 cm. long and from 1.5 to 4.0 cm. interior diameter according to the size of the animal. For large animals two Liebig condenser jackets connected end to end make a convenient tube. The other end of this tube was connected air tight with the cannula tied into the trachea. Near both ends and at the middle of the tube were adjustable escape vents. Near the tracheal end of the tube was another opening to which a bottle containing ether was connected by a short piece of rubber tubing. When the bottle was inverted a few drops of anaesthetic fell into the tube.

desired rate of pulmonary ventilation simultaneously with a sufficient movement of the lungs to inhibit through vagus apnoea all spontaneous respiratory effort by the subject. The necessity of producing a considerable movement of the lungs simultaneously with a very slight ventilation with fresh air, when very slow heart-rates are to be induced, arises from the fact that otherwise the venous condition of the arterial blood under slight aeration induces a hyperpnoea which sympathetically accelerates the heart-rate. By means of this apparatus the heart-rate can be regulated to any desired rhythm from below 50 up to more than 200 beats per minute. In our hands it has never induced cardiac tetanus even when worked to the utmost. In all experiments in which excessive
ventilation was maintained for any considerable period shock developed. On the other hand shock never developed, even when the period of observation lasted for the greater part of a day, in those experiments in which excessive ventilation and tachycardia were maintained for only a few minutes at a time, and in which the heart-rate was then slowed down to a normal rhythm by diminished ventilation,—providing sufficient care was exercised not to carry out the latter process so rapidly as seriously to impair the oxygen supply.

When a normal slow heart-rate was desired, the middle vent was opened slightly, and the bellows was worked at about twenty strokes per minute of moderate amplitude. When a gradually accelerating heart-rate was desired, the vent near the trachea was opened and the middle vent closed without changing the rate and depth of respiration. When tachycardia was desired, the tracheal vent was opened widely, and the bellows was worked so as to give as full and as rapid a respiration as possible. Under these conditions a very thorough pulmonary ventilation was effected. In dogs of moderate size the heart-rate within two to four minutes could be accelerated from 50 or 60 up to 180 or 200.

When a restoration of the slow heart-rate was desired, the middle vent alone was opened, and this vent only slightly. At first barely sufficient respiration was given to keep the lungs distended. The exhalation of CO₂ was thus reduced, and a condition afforded in which the blood and tissues gradually recuperated their supply. During this procedure arterial pressure and the amplitude of the heart-beat (as shown either in the volume curve or in the pulse curve) were watched with the utmost care. A diminution in either of these functions was taken as an indication that the oxygen supply was being reduced beyond the point of safety. Several times in our earlier experiments it happened that during this procedure, after an extreme and unusually prolonged excessive ventilation, the amplitude of the heart-beat narrowed, arterial pressure fell, and the subject came to the point of death without the slightest spontaneous respiratory effort, without any marked preliminary slowing of the heart-rate, and without a rise of arterial pressure. From these observations it appears that lack of oxygen is not the cause of the symptoms characteristic of asphyxia. Lack of oxygen apart from excess of CO₂ is not a stimulus. It merely paralyzes.

When care was taken not to diminish the ventilation beyond the
point at which the arterial blood was only slightly darkened in color, the process of restoring the CO₂ content of the blood and regaining a slow heart-rate required a half hour or more according to the extent of the acapnia previously induced. From a normal rate the heart could for a few minutes at a time be slowed down to rates of only 20 to 30 beats per minute. This object was accomplished by opening only the vent next the bellows. In this case nearly all of the fresh air escaped even when the bellows was worked with vigor. The dead air in the tube was merely moved back and forth between the tracheal end of the tube and the lungs. The pulmonary ventilation was thus reduced almost to nil, but a sufficient movement of the lungs was effected to induce vagus apnoea. Spontaneous respiratory movements sometimes occurred in spite of this inhibition. Arterial pressure was maintained in spite of the bradycardia. From these observations, coupled with those described in the preceding paragraph, it appears that the excess of CO₂ in the blood is the stimulus to the respiratory, cardio-inhibitory, and vaso-motor centres which causes the symptoms characteristic of asphyxia.

Including both our earlier and later experiments on artificial respiration with open thorax, thirty dogs were used. In connection with five of the later experiments blood gas analyses were performed. The following is an example of one of these later experiments.

Experiment of July 3, 1906.—Dog of 22.0 kilos. Morphine and ether, Tracheotomized and thorax opened at 10.10, cardiometer placed on the ventricles, and artificial respiration maintained with the apparatus shown in Fig 2. The graphic records obtained during the period of observation from 10.00 A.M. to 5.15 P.M. will be reproduced in a later paper. They consist of the four-fold repetition of such a record as that in Fig. 1 from 12.45 to 1.15. The data obtained are summarized in Table II, p. 150.

In this experiment an example is afforded of the prevention of shock by care in the administration of artificial respiration. The intervals of excessive ventilation were never prolonged beyond a few minutes. Seven hours after the opening of the thorax, and prior to the last interval of excessive ventilation, the animal was in such good condition that it might easily have been restored to normal life, if antiseptic precautions had been employed. Throughout the seven hours of observation the heart-rate was varied at the...
will of the operator at the bellows with the ease and almost with the precision that the rate of the ticking of a clock is varied by changes in the length of its pendulum.

**TABLE II.**

**DATA OBTAINED IN EXPERIMENT OF JULY 3, 1906.—See p. 149.**

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>O₂</strong></td>
<td><strong>CO₂</strong></td>
<td><strong>mm. of Hg.</strong></td>
<td></td>
</tr>
<tr>
<td>10.00</td>
<td>20.1</td>
<td>42.6</td>
<td>68</td>
<td>95</td>
</tr>
<tr>
<td>10.30</td>
<td>....</td>
<td>....</td>
<td>84</td>
<td>105</td>
</tr>
<tr>
<td>10.45</td>
<td>....</td>
<td>....</td>
<td>120</td>
<td>110</td>
</tr>
<tr>
<td>11.15</td>
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<td>....</td>
<td>84</td>
<td>120</td>
</tr>
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</tr>
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<td>35.2</td>
<td>96</td>
<td>110</td>
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<td>75</td>
</tr>
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<td>2.15</td>
<td>....</td>
<td>....</td>
<td>60</td>
<td>105</td>
</tr>
<tr>
<td>2.16</td>
<td>....</td>
<td>....</td>
<td>200</td>
<td>85</td>
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<tr>
<td>2.45</td>
<td>....</td>
<td>....</td>
<td>90</td>
<td>90</td>
</tr>
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<td>3.30</td>
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<td>....</td>
<td>72</td>
<td>100</td>
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<td>5.00</td>
<td>....</td>
<td>....</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>5.15</td>
<td>....</td>
<td>....</td>
<td>220</td>
<td>60</td>
</tr>
</tbody>
</table>

**SHOCK AND ITS PREVENTION UNDER THE SAUERBRUCH-BRAUER METHOD OF RESPIRATION.**

The first clear indication of the relation of excessive pulmonary ventilation to the development of shock, and the starting-point for all of our later investigations in this field, occurred in connection with experiments in which, after the opening of the thorax, a natural respiration of compressed air was maintained. This method of respiration was originated by Sauerbruch;* and simplified by

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*Sauerbruch: Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie, 1904, xiii, art. xvii.
At the time of its publication, three years ago, it excited a very general interest both among surgeons and experimenters. By the employment of this method in either its original or its modified form, it seemed not too much to hope that the thoracic viscera would become almost as readily accessible as a field of surgical operation as are those of the abdomen. For purposes of experimentation it appeared to conserve more nearly normal conditions after pneumo-thorax than are afforded by artificial respiration. Several American investigators who have tried the Brauer method have found, however (as they have verbally informed the writer), that the results obtained are in fact much less satisfactory than are those afforded by artificial respiration. Likewise in Germany Sauerbruch and his adherents have found the Brauer modification unsatisfactory, although they have not succeeded in proving any essential difference either theoretical or practical between the original and the modified method. Seidel has observed that under the "Uberdruckverfahren" of Brauer tracheotomized animals fare much worse than those which breathe by mouth and nose into the pressure chamber.

In our experience, on the contrary, the first trial of the Brauer method shortly after its publication was strikingly successful. When the thorax was opened, the trachea was connected with a large gasometer by a piece of rubber hose two centimetres in diameter and a metre in length. At the point where the hose connected with the gasometer the air was allowed to escape through a side tube leading to a Mueller valve adjusted to maintain the air in the system at a positive pressure of 11-13 cm. of water. The lungs were thus kept at a nearly normal distention, and the respiratory movements of the diaphragm and the thoracic walls were effective. Throughout and up to the end of the six hours of the experiment the animal maintained a deep steady respiration, high blood pressure, and normal heart-rate. Yet in addition to the extensive initial operation, a plethysmograph was placed about the ventricles of the heart, another upon the right auricular appendage, and a catheter was inserted into the left ventricle through the carotid. Three of the graphic records obtained in this experiment were published in our earlier paper.

Equally signal failures were the next three experiments. Yet

52 BRAUER: Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie, 1904, xiii, art. xviii.
53 SEIDEL: Ibid., 1907, xvii, art. xxiv (complete bibliography).
the operative and experimental procedures were the same as in the first experiment, except that the apparatus supplying air was improved (as we then supposed) by removing the side tube leading to the Mueller valve from the end of the hose connected to the gasometer and inserting it at the junction of the hose with the tracheal cannula. In this manner we thought to afford a much fresher supply of air to the lungs; for if we consider that under the earlier arrangement the hose constituted merely an elongation of the trachea, it is evident that by this change the stationary air was diminished and the pulmonary ventilation increased. Under these conditions three successive animals, each a fair-sized and vigorous dog, collapsed rapidly. The heart-rate rose in the course of the first half hour to 180 or more per minute. The amplitude of the pulse and volume curves was progressively diminished. In two cases arterial pressure began to fall after two hours. The pulse slowed somewhat, but was still rapid. The amplitude of the heart-beat and pulse was not recovered. The respiration became shallow. At the end of three hours the animals were in a dying condition. In another case the animal ceased to breathe after an hour and a half, although the arterial pressure had not fallen and the pulse was about 200 per minute. Indeed, a tendency to apnoea is a constant and significant symptom accompanying tachycardia. Both symptoms are due to a subnormal CO₂ content in the blood supply to the cardiac and respiratory centres.

A fifth trial of the Sauerbruch Brauer method yielded by accident the key for the adjustment of the method to the respiratory needs of an animal. The conditions of the experiment were the same as in the three preceding. Within half an hour the animal had developed a marked tachycardia. Believing that such a failure as the experiment promised to be might as well be ended immediately, one of us turned off the stop-cock on the gasometer, to which was connected the hose leading to the tracheal cannula. The lungs were thus left distended, and the animal for a number of successive respirations repeatedly inspired and expired the same air so far as the respiratory movements were effective. To our astonishment the heart-rate immediately slowed down. The volume curve of the heart and the pulse curve regained their normal amplitude. When, however, the fresh air was turned on again by reopening the stop-cock on the gasometer, the rhythm of beat, after remaining for a few minutes normal, again increased in rapidity.
Excessive pulmonary ventilation was thus in these experiments also indicated as the cause of tachycardia and of the development of shock. In the long series of experiments which followed and which form the second series in our previous paper, the heart-rate was regulated by means of the apparatus shown in Fig. 3.

54 The T-tubes were obtained from a plumber. Pieces of gas pipe 5 cm. in length were screwed into their openings.
With this apparatus variations in the pulmonary ventilation were effected in a very simple manner. When a full ventilation was desired the Mueller valve near the gasometer was closed and that near the trachea opened. When a regulated ventilation was desired the former was opened and the latter nearly or completely closed. A further regulation was obtained by means of the stopcock, which opened from the gasometer into the etherizing flask.

**TABLE III.**

**To accompany Figure 4.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Arterial blood gases.</th>
<th>Heart-rate per minute.</th>
<th>Amplitude of beat.</th>
<th>Output of left ventricle per minute.</th>
<th>Arterial pressure, mm. of Hg.</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volumes &amp; Per cent CO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.15</td>
<td>17.1 &amp; 41.3</td>
<td>60</td>
<td>27-40</td>
<td>1050</td>
<td>130</td>
<td>Regulated ventilation.</td>
</tr>
<tr>
<td>3.55</td>
<td>19.5 &amp; 29.4</td>
<td>150</td>
<td>12</td>
<td>900</td>
<td>105</td>
<td>Full</td>
</tr>
<tr>
<td>4.10</td>
<td>... &amp; ...</td>
<td>90</td>
<td>12-28</td>
<td>870</td>
<td>125</td>
<td>Regulated</td>
</tr>
<tr>
<td>4.30</td>
<td>... &amp; ...</td>
<td>160</td>
<td>11-14</td>
<td>960</td>
<td>115</td>
<td>Full</td>
</tr>
<tr>
<td>5.05</td>
<td>... &amp; ...</td>
<td>70</td>
<td>15-33</td>
<td>755</td>
<td>130</td>
<td>Regulated</td>
</tr>
<tr>
<td>51.5</td>
<td>... &amp; ...</td>
<td>100</td>
<td>16</td>
<td>800</td>
<td>110</td>
<td>Full</td>
</tr>
<tr>
<td>5.35</td>
<td>... &amp; ...</td>
<td>150</td>
<td>11</td>
<td>825</td>
<td>70</td>
<td>&quot;</td>
</tr>
<tr>
<td>6.15</td>
<td>... &amp; ...</td>
<td>160</td>
<td>8</td>
<td>640</td>
<td>40</td>
<td>Shock.</td>
</tr>
</tbody>
</table>

Even under the fullest ventilation by this method the acceleration of the heart-rate was relatively slow as compared with that attainable under artificial respiration. At the first attempt an increase in half an hour from 70 or 80 up to 150 beats per minute was the usual acceleration. After the animal had once become distinctly acapnic the change from a slow to a rapid heart-rate could be effected much more quickly. The slow pulse induced by diminished ventilation after an interval of acapnia was always characterized by an alternation of slow full beats during the respiratory pause and quicker narrower beats during inspiration.

On the question why an animal after the opening of its thorax should breathe itself into acapnia we have as yet no sufficient explanation. It appears probable that an exhalation of CO₂ from the pleura may occur. Even if this exhalation occurs, however, it
Acapnia and Shock.

does not explain the failure of the normal adjustment of pulmonary ventilation to the respiratory needs of the animal. This matter will require further investigation. The point to be emphasized here is the fact that throughout our experiments, when acapnia was altogether prevented, shock never developed even when the period of observation lasted all day.

Including both our earlier and later experiments with this method of respiration twenty-five dogs were used. In connection with three of the later experiments blood gas analyses were performed. Fig. 4 and the analytical data accompanying it afford an example of one of these later experiments.

**Summary.**

1. In dogs under artificial respiration the development of shock is dependent not upon the extent of the injuries and the intensity of the stimulations to afferent nerves, but upon the rate of pulmonary ventilation.

2. The hypothesis is presented that acapnia (diminished CO₂ in the blood and tissues resulting from hyperpnoea and from exhalation of CO₂ from exposed viscera) is the cause of surgical shock.

3. The literature of CO₂ as a hormone is reviewed in order to show that the failure of the circulation and of the nervous system in shock and the cessation of respiration in apnoea vera must logically be referred to the same cause, — acapnia.

55 The numerals refer to the sections summarized.
4. Experiments are described in which by the effects (probably upon the centres in the spinal bulb) of a sudden great diminution in the CO$_2$ content in the arterial blood the heart-rate was increased up to the point of cardiac tetanus, and death resulted.

5. In experiments in which less extreme but still excessive artificial respiration was maintained for an hour or more a condition of typical surgical shock developed.

6. By regulating the rate of pulmonary ventilation by the method here described the heart can be adjusted to any desired rate of beat.

7. The reason for the unsatisfactory results obtained with the Sauerbruch-Brauer methods of respiration is to be found in the development of acapnia. Prevention of acapnia by the method here described prevents the development of shock.

The next three papers of this series, for which the data are already complete, will deal with the production and prevention of shock from exposure of the abdominal viscera, and from the hyperpnoea of pain and of ether excitement.