A post-graduate lecture on the influence of the arterioles in relation to various pathological conditions / by Sir George Johnson.

A Post-Graduate Lecture

ON

THE INFLUENCE OF THE ARTERIOLES IN RELATION TO VARIOUS PATHOLOGICAL CONDITIONS.

BY

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THE INFLUENCE OF THE ARTERIOLES IN RELATION TO VARIOUS PATHOLOGICAL CONDITIONS.

The Structure and Function of the Arterioles.—Apnœa (Asphyxia).—Anæsthesia by Nitrous Oxide and by Nitrogen.—The Pathology of Choleraic Collapse.—Variations of the Pulse.—The Cardio-vascular Changes in Bright's Disease.—Raynaud's Disease.

THE most important and fruitful addition to our knowledge of the circulation of the blood since the time of Harvey has been the discovery of the muscularity of the middle coat of the arterioles and the stopcock function of these small vessels in regulating and controlling the amount of blood transmitted to the capillaries and veins.

In 1840 Henle[1] described the circular muscular fibres in the middle coat of the arterioles and demonstrated their identity with unstriped muscular fibre in other parts of the body.

In 1852 M. Claude Bernard[2] published the first of his series of observations on the influence of the vasomotor nerves and the arterioles. His researches, together with those of Brown-Séquard, Waller, Ludwig, and others, have proved that the function of the arterioles is that of regulating the blood supply to the various organs and tissues; while some pathological phenomena to be presently described clearly indicate that the impediment caused by a general contraction of the systemic or the pulmonary arterioles is more than equal to the propelling power of the left or the right ventricle respectively.

My main object in the present communication is to prove that a due appreciation of the action of the arterioles is essential for a correct interpretation of some highly interesting and important pathological phenomena.

APNŒA OR ASPHYXIA.

There are few subjects which have given rise to so many conflicting statements and opinions as that of the immediate cause of death by deprivation of air. The application of the term asphyxia, which signifies an arrest of the pulse, to a condition whose primary cause is impeded or suspended breathing—apnœa[3]—has been one source of confusion which I will avoid in the present communication.

Dr. John Reid, in his paper "On the Order of Succession in which the Vital Actions are Arrested in Asphyxia,"[4] has given a very complete account of the various attempts which had been made to explain the phenomena previous to the year 1840, when his paper on the subject was read at the British Scientific Association. He shows that before his own researches began no satisfactory explanation had been given of the impeded circulation through the lungs, and the consequent distension of the right side of the heart in the last stage of apnœa.

By making animals breathe nitrogen Dr. Alison and Dr. Reid proved that the impeded pulmonary circulation "is dependent upon the cessation of the chemical changes between the blood and atmospheric air in the lungs, and not upon the arrestment of the mechanical movements of the chest," as some of their predecessors had supposed, and they suggested that the arrest occurs in the pulmonary capillaries. This explanation, before the discovery of the structure and function of the arterioles, appeared sufficiently plausible. The most interesting original observation made by Dr. Reid was that of the increased pressure in the systemic arteries during the earlier stages of apnœa. This he explained by "an impediment to the passage of venous blood through the capillaries of the systemic circulation." As Dr. Reid's experiments were conducted, the observation of the blood pressure was somewhat interfered with by the sudden variations which resulted from the violent respiratory efforts of the suffocated animals; but Mr. Erichsen[5] subsequently, in a series of highly instructive experiments, got rid of this disturbing element by dividing the spinal cord as near to the cranium as possible, the animals then being kept alive for a time by artificial respiration. The results obtained by this method of experimenting were in entire agreement with those of Dr. Reid.[6]

It is a well-known fact that newly-born animals bear the exclusion of air much longer than the same class of animals a few days older. Thus Dr. M. Foster says,[7] "while in a full-grown dog recovery from drowning is unusual after one minute and a-half, a newborn puppy has been known to bear an immersion of as much as fifty minutes;" and he goes on to say: "The cause of this difference lies in the fact that in the quite young or rather just born animal the respiratory changes of the tissues are much less active. These consume less oxygen, and the general store of oxygen in the blood has a less rapid demand made upon it." There is probably some truth in this statement, but the explanation ignores the fact that in these animals for some days after birth, and so long as their eyes remain closed, the foramen ovale is open, so that when air is excluded from the lungs the blood passes directly, as in the fœtus, from the right to the left side of the heart, and so escapes the controlling influence of the pulmonary vessels.

Mr. Erichsen performed some interesting experiments on these newly-born animals, and found that not only did the circulation continue much longer after the exclusion of air than in older animals, but when the chest was opened after death there was no distension on the venous side of the heart, and the amount of blood on the two sides was nearly equal.

The description and explanation of the process of apnœa which had been published by Dr. John Reid and Mr. Erichsen were generally accepted by physiologists, and were repeated in all the textbooks until the year 1867, when Professor Burdon Sanderson, in his Croonian Lecture at the Royal Society,[8] made the following statement: "It may be concluded that the extraordinary elevation of arterial pressure which has been long known to occur during the second minute in death from apnœa is not due, as was supposed by Dr. Alison and Dr. John Reid, to obstruction of the capillary vessels, either pulmonary or systemic, but to the violence of the respiratory efforts. The cavity of the chest being closed, the force exercised by the respiratory muscles expresses itself in variations of tension of the enclosed air, which are communicated through the intrathoracic arteries to those outside of the chest, producing those violent oscillations of the dynamometer which have been referred to. In support of this inference it was shown that in an animal under the influence of worara[9]—when all respiratory movement ceases while those of the heart are unaffected—the process of apnœa is not only of greater duration, but is not attended by any of those greater disturbances of the circulation which have been hitherto attributed to capillary obstruction. The gradual extinction of the force of the contractions of the heart is indicated by a slow and uninterrupted subsidence of the arterial pressure."[10]

In the *Handbook for the Physiological Laboratory*, published in 1875, Dr. Sanderson states that after death from apnœa "it is always found that all the heart's cavities are filled to distension, the quantities in the right and left cavities respectively usually being to each other in the proportion of about two to three."[11] The inaccuracy of this statement may be proved by an experiment which need occupy only a few minutes. I have been present on two occasions when the heart of a dog has been examined immediately after death from a ligature on the trachea. In the case of a large dog 2 ounces of blood gushed from the distended right cavities, while 2½ drachms trickled from the flaccid left side. In a small dog the distended right side of the heart contained 5½ drachms of blood, the left a quarter of a drachm.[12]

What, then, is the explanation of the results obtained by Professor Sanderson? Simply this, that the dose of worara which he administered to the dogs—one-tenth of a gramme—was sufficient to paralyse, not only the voluntary muscles, but also the muscular walls of the arterioles, both systemic and pulmonary, and thus to render them powerless to impede or to regulate the onward movement of the blood.

Professor Rutherford, in a lecture on the circulation,[13] says that "the dose of curara should be just sufficient to paralyse the voluntary muscles; if the dose be excessive the vaso-motor nerves are also paralysed. The amount given should be 12 milligrammes for a small dog, and 18 milligrammes for a large one." Thus Professor Sanderson's dose of one-tenth of a gramme (that is, 100 milligrammes) is more than five times the amount which Professor Rutherford employs for a large dog. I have at different times witnessed experiments which clearly show that when a moderate dose of curara is injected the results of apnœa are essentially different from those described by Professor Sanderson, while an excessive dose gives results which are in entire agreement with his.

I will now describe the most interesting and conclusive of these experiments.

In 1873 I witnessed a very instructive experiment by Dr. Rutherford when he was Professor of Physiology in King's College. Into the trachea of a large dog, previously anæsthetised, a tube was tied and connected with a bellows for artificial respiration. The voluntary muscles were then paralysed by a moderate dose of curara, and the animal was kept alive by artificial respiration. The sternum and portions of the ribs were removed, and the pericardium opened so as to expose the anterior surface of the heart. One common carotid was divided, and a dynamometer tube connected with a kymograph was tied into its proximal end. Artificial respiration being suspended there was first a steady rise of pressure in the carotid, and soon distension and dilatation of

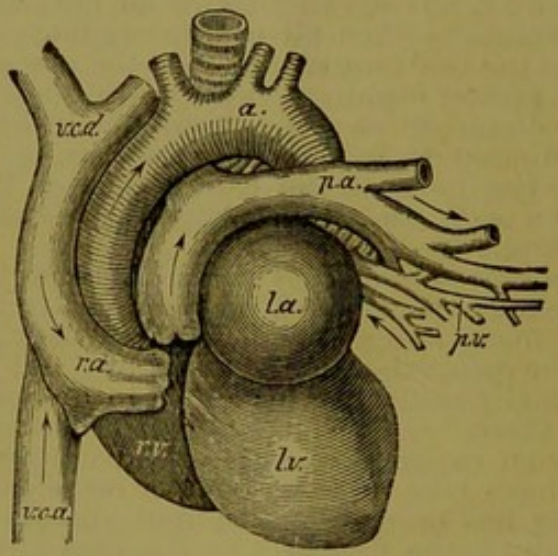

Fig. 1 represents the distension of the left cavities of the heart and aorta in the first stage of apnœa (asphyxia). *l.a.*, Left auricle; *l.v.*, left ventricle. Both greatly distended, the former like a smooth india-rubber ball. *a.*, Aorta distended; *p.a.*, pulmonary artery; *p.v.*, pulmonary vein; *r.a.*, right auricle; *r.v.*, right ventricle; *v.c.d.*, descending vena cava; *v.c.a.*, ascending vena cava. The right cavities of the heart, the pulmonary artery, and the systemic veins are in a state of normal fulness. The right ventricle is partly overlapped by the distended left.

the *left* cavities of the heart (Fig. 1), then a rapid fall of pressure, distension and dilatation of the *right* cavities, with collapse and almost complete emptying of the left side (Fig. 2).

The explanation of the facts is briefly this. Venous blood passing into the systemic arteries excites through the vasomotor ganglia, nerves, and centres,[14] contraction of the arterioles, with resulting high arterial tension and distension of the left side of the heart from backward pressure. When the deoxidation of the blood exceeds a certain degree,[15] the vasoconstrictors of the lungs impede the passage of the blood, the result being that the left side of the heart receives but little blood, and that of a venous character, the systemic

arterial pressure falls, while the right cavities, the large veins, and the pulmonary artery are distended with blood. This unequal distribution of blood, which is invariably found when the chest is opened soon after death from apnœa, was, in the course of Dr. Rutherford's experiment, plainly seen to occur during the lifetime of the animal.

The suggestion that the empty condition of the left ventricle after death from apnœa is the result of rigor mortis is obviously not in accordance with the facts thus demonstrated. And it is evident that in Dr. Rutherford's experiment the increased arterial pressure during the first stage of apnœa was not the result of "violent respiratory efforts."

Some physiologists assert that in the final stage of apnœa the systemic arterioles dilate in consequence of a supposed exhaustion of the vasomotor centre by deoxidised blood; of

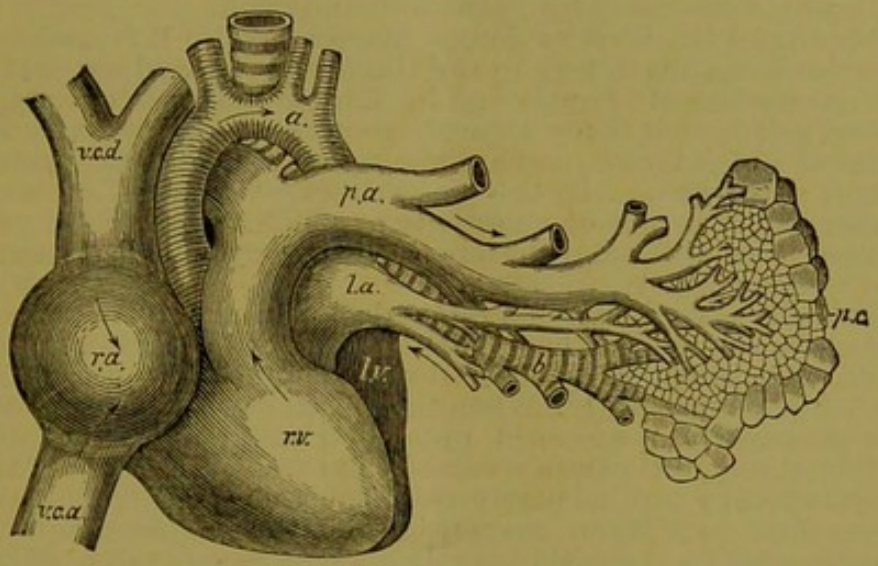

Fig. 2 represents the distension of the right cavities of the heart, of the pulmonary artery, and the large systemic veins in the final stage of apnœa (asphyxia). The letters have the same significance as in Fig. 1. In addition, *p.c.* indicates the anæmic condition of the pulmonary capillaries; *b.*, left bronchus. The right auricle and ventricle and the pulmonary artery are fully distended, the auricle having the form and smoothness of a distended ball, while the left cavities of the heart and the aorta are collapsed and nearly empty.

this, however, there is no proof, and the assumed condition would not explain the facts. Dr. M. Foster says:[16] "The blood pressure, in spite of the continued arterial contraction, begins to fall, since less and less blood is pumped into the arterial system." The condition of the heart's cavities soon after death from apnœa clearly indicates that the immediate cause of death is primarily the arrest of the pulmonic, and, as a consequence, that of the systemic circulation. It will be seen that there are two distinct stages in the process of apnœa: (1) that of systemic arterial obstruction, with distension of the left cavities of the heart; (2) that of pulmonary arterial obstruction, with distension of the right cavities. The two sides of the heart, therefore, are never fully dis-

tended at the same time, since in the final stage of apnœa, while the distension of the right cavities is rapidly increasing, that of the left is with equal rapidity passing away. It is also evident that the contraction of the pulmonary arterioles in the final stage has the double effect of increasing the resistance to the propelling force of the right ventricle while the walls of the heart are weakened by the scanty supply of deoxygenised blood to the coronary arteries.

It has often been noted after death from apnœa that more or less numerous ecchymoses appear beneath the pleura and pericardium. These are obviously the result of backward engorgement of the bronchial and coronary veins and capillaries which share in the distension of the whole systemic venous system.

We have now to show that when the arterioles are paralysed by an excessive dose of curara or by other substances which are known to have that effect the results are identical with those described by Professor Sanderson.

My friend Mr. Charles James Martin, M.B., B.Sc., who is now teaching physiology in the University of Sydney, while Demonstrator of Physiology in King's College four years since, performed, at my request, some experiments, the results of which throw much light upon the complex phenomena of apnœa. All the animals experimented on were under the influence of anæsthetics, which, while they prevented pain, did not interfere with the physiological results of the experiments.

Into the peritoneum of a cat a decigramme of curara was injected, the animal being kept alive by artificial respiration. A manometer connected with a kymograph was introduced into one carotid. When the respiration was suspended the pressure in the carotid immediately began to fall and artificial respiration was resumed to prevent the arrest of the circulation by cardiac paralysis. The same result followed more than once upon suspension of the respiration. At length after an interval of nearly an hour, suspension of respiration was accompanied by a rise of pressure in the carotid; and the heart having been exposed there was seen to occur the usual distension, first of the left cavities, then of the right, with shrinking of the left. In this experiment the excessive dose of curara paralysed the arterioles and weakened the heart. The suspension of respiration still further weakened the heart and lessened the arterial pressure. After a time a portion of the curara was eliminated, probably by the kidneys, a large amount of urine having been passed upon the operating table, and then the usual results of apnœa, with a moderate dose of curara, were observed.

A moderate dose of curara was injected into a cat. Suspension of respiration was followed by the usual rise and subsequent fall of the systemic arterial pressure. The circulation having been restored by artificial respiration, sulphate of atropine was injected into the jugular vein, after which the arrest of the breathing caused no rise of pressure in the carotid, and when the heart was exposed no unequal distension of its cavities was observed. The arterioles, both systemic and pulmonary, were paralysed by the atropine.

Into the trachea of a small dog, prepared with the chest and pericardium open, and kept alive by artificial respiration, a glass tube was introduced, through which pure nitrous

oxide gas was passed into the lungs, whilst the expired gases escaped into the air. As usual in cases of apnœa, first the left then the right cavities of the heart became distended, and in one minute the heart's action had nearly ceased, with enormous distension of the right side. Then without loss of time inhalation of nitrous oxide, mixed with the vapour of nitrite of amyl, was substituted for the pure N_2O, by means of a two-way stopcock, and the result was that almost immediately the distension of the right cavities began to subside, and in two minutes they had nearly regained their normal size. In this experiment we have evidence that the contraction of the pulmonary arterioles—a result of deprivation of air—which caused the distension of the right cavities of the heart was quickly removed by the paralysing effect of the nitrite of amyl on the arterioles, atmospheric air being all the time strictly excluded by N_2O.

Some facts which tend to complete and confirm the theory of apnœa which I have here set forth yet remain to be mentioned. It has been noticed by different experimenters that during the earlier stage of apnœa the resistance resulting from the contraction of the systemic arterioles has a retrograde influence, not merely on the left side of the heart, as we have seen, but also upon the pulmonary veins, and even so far as the pulmonary artery, in which a slight increase of pressure occurs almost if not quite simultaneous with the much greater increase of pressure in the systemic arteries. In the final stage of apnœa, while the pressure in the systemic arteries is falling to zero that in the pulmonary artery is continually rising—an increase which can be explained only by the contraction of the pulmonary arterioles. The anæmic condition of the pulmonary capillaries which is always observed when the lungs are examined immediately after death indicates that the mass of the blood has been arrested before it has reached the capillaries, and when the lungs are exposed during life they are found to become visibly paler during the final stage of apnœa. The extreme collapse of the lungs when the chest is opened after death is a result of the bloodless condition of their minute vessels.

Dr. Rose Bradford and Dr. Percy Dean[17] have proved the existence of pulmonary vasomotor nerves, and that the pulmonary circulation is comparatively independent of the systemic, but they say "it is probable that the vasomotor mechanism is but poorly developed as compared with that regulating the systemic arteries." It might with equal reason be suggested that the muscular walls of the right ventricle are "but poorly developed," since they are unable to overcome the resistance resulting from the contraction of the pulmonary arterioles in the final stage of apnœa. That the pressure in the pulmonary artery and its branches can never equal that in the aortic system is obvious from anatomical considerations alone, but it may be safely assumed that the vessels of the lung, through which all the blood in the body has to pass, have the same regulating and resisting power compared with the force of the right ventricle as that possessed by the systemic vessels in relation to the left ventricle; and I am convinced that much of the confusion and contradiction which appear in the explanation of the phenomena of apnœa given by different physiologists is a result of their ignoring the influence of the pulmonary arterioles.

It is certain that by no experiment that has hitherto been devised can the actual propelling force of the right ventricle or the resisting power of the pulmonary arterioles be even approximately determined; and this for the obvious reason that any impediment to the flow of blood through the lungs, by mechanical compression of the pulmonary artery or its branches, weakens the heart by lessening the blood supply to the coronary arteries. So in the last stage of apnœa, when Mr. Martin has found the pressure in the pulmonary artery to be nearly doubled while that in the carotid is rapidly falling, the heart is weakened, not only by the small amount of blood which reaches its nutrient vessels, but by the fact that even that small supply of blood is entirely deoxidised. The convulsions which always precede death from apnœa when the muscles have not been paralysed by curara, and which tend to increase the distension of the right side of the heart by the pressure of the convulsed muscles on the veins, are the result of cerebral anæmia, the small amount of blood which reaches the brain being also entirely deoxidised. These convulsions are similar to those which result from a copious and rapid hæmorrhage from embolic plugging of the pulmonary artery, from the forcible entrance of air into a vein, or from ligature of the carotid and subclavian arteries.[18]

Summary of Conclusions relating to Apnœa.

That the immediate cause of death from apnœa is the arrest of the pulmonary circulation is proved by the following facts: 1. When the chest of an animal is opened immediately after death by apnœa, the right cavities of the heart are found enormously distended while the left are comparatively empty. 2. When the heart of an animal is exposed during the progress of apnœa, the right cavities are seen to become distended, while the left cavities, which had been previously gorged, are rapidly unloading themselves. The obstruction in the lungs which causes the distension of the right cavities lessens the blood supply to the left. The two sides of the heart, therefore, are never fully distended at the same time. 3. In the final stage of apnœa there is a continuous rise of pressure in the pulmonary artery, while the systemic arterial pressure is falling. 4. That the arrest of the circulation through the lungs is caused by contraction of the pulmonary arterioles appears to be proved by the influence of agents which are known to paralyse those vessels—namely, nitrite of amyl, atropine, and an excessive dose of curara, the result being that deprivation of air is unattended by distension of the right cavities of the heart and other evidence of obstructed pulmonary circulation, the life of the animal is prolonged for several minutes, and death ultimately results from the toxic action of deoxodised blood upon the cardiac and nervous tissues. 5. It is an acknowledged fact that these paralysing agents act alike upon the systemic and the pulmonary arterioles, but the successive phenomena of apnœa are inconsistent with the idea that the distension of the right side of the heart is a result of systemic arterial obstruction acting backwards through the left side of the heart and the lungs. One result of such a retrograde influence would obviously be engorgement of the pulmonary capillaries, a condition the reverse of that which is found immediately after death from apnœa.

The Physiology of Nitrous Oxide Anæsthesia.

In the phenomena of apnœa with the resulting rapid impediment to, and even the complete arrest of, the circulation which occur when nitrous oxide gas is inhaled as an anæsthetic, we have an interesting confirmation of the results obtained by excluding air from the lungs; and on the other hand the knowledge obtained by experiments on animals killed by apnœa enables us more completely to interpret the facts of nitrous oxide anæsthesia.

Through the courtesy of the staff of the Dental Hospital in Leicester Square I have on many occasions during the last few years had the opportunity to observe the phenomena which result from the inhalation of the gas, and, in particular, I have carefully noted the changes in the character of the pulse during the successive stages of the inhalation.

In the early stage the respiration is deepened and quickened, while the pulse, which is usually quickened, always becomes fuller and firmer. A few seconds later the pulse is less full and more compressible, and if the inhalation be continued, the pulse becomes so small and feeble as to be scarcely, or even not at all, perceptible; at the same time the breathing is stertorous, the features are livid, and the pupils dilated, while there is more or less jactitation of the extremities, and often general tonic contraction of the muscles. Micturition rarely occurs, defæcation still more rarely. That these symptoms are of an epileptiform character is, I think, unquestionable. The convulsions are sometimes so violent, especially in children, as to throw the patient from the chair.

After the readmission of air the pulse again becomes for a time full and strong, and less frequent, the lividity passes away, and consciousness quickly returns. There is obviously a very close resemblance between these symptoms and those which result from apnœa. When an animal is killed by inhaling nitrous oxide gas convulsions always precede death, and when the chest is opened immediately after death, the right side of the heart is found to be greatly distended while the left is nearly empty, the blood on the two sides of the heart being equally dark. The lungs are pale, their minute vessels are bloodless, and the lungs consequently collapse into a very small space when the chest is opened. These appearances are identical with those which are found after death from apnœa. What, then, is the explanation of the phenomena? It has been ascertained that at the temperature of the body nitrous oxide gives up no oxygen to the blood or the tissues. The gas rapidly replaces the oxygen in the blood and in the tissues; the full and strong pulse, the result of contraction of the arterioles excited by the passage of venous blood into the systemic arteries, is the counterpart of the high pressure in the arteries of animals deprived of air, while the small and weak pulse which follows, like the rapid fall of pressure in the advanced stage of apnœa, is the result of the impeded flow of blood through the lungs caused by contraction of the pulmonary arterioles, the heart at the same time being weakened by the small amount of blood, and that unoxygenised, which passes into its nutrient vessels. Again the convulsive movements which are common to the two classes of cases admit of the same physiological explanation. When in an animal the inhalation of the gas is

pushed to a fatal termination, convulsions are as constant and as violent as when death is caused by a ligature on the trachea. The spectroscopic examination of the blood immediately after death shows that the hæmoglobin has been entirely deoxidised.

I find that some anæsthetists who are daily occupied in the beneficent work of administering nitrous oxide, with perhaps a natural unwillingness to admit that the freedom from pain which they ensure is the result of replacing vital air by an azotic gas, maintain that apart from or in addition to its acknowledged deoxidising effect nitrous oxide has a special anæsthetic influence. Of this specific action, however, so far as I can learn, they adduce no proof. True Dr. F. Hewitt states[19] "that the anæsthesia is not due to asphyxia is probable from the fact that it is possible to secure absolute unconsciousness to pain, muscular relaxation, etc., from nitrous oxide mixed with such a proportion of oxygen that the development of obvious asphyxial phenomena is rendered physiologically impossible." Now in making this statement Dr. Hewitt has not taken into consideration the influence of the great solubility of nitrous oxide in the blood as compared with that of oxygen or nitrogen. If a mixture of nitrous oxide with 10 or 15 per cent. of oxygen were inhaled for a minute or so and if the expired gases were analysed it would be found that the relative amount of nitrous oxide and of oxygen has undergone a change, the nitrous oxide being less and the oxygen more in proportion than before the mixed gases were inhaled. The explanation is that a larger proportion of nitrous oxide than of oxygen is for a time retained in the blood, partly in solution and partly in a state of loose combination, and this excess deoxidises the hæmoglobin sufficiently to effect anæsthesia without the development of so-called asphyxial symptoms.

Then it is to be observed that the mixture of oxygen with nitrous oxide considerably retards the production of deep anæsthesia. Thus Dr. Hewitt states that while the average period of inhalation required to produce deep anæsthesia with nitrous oxide alone is 51 seconds[20] the mixture with oxygen requires that the inhalation should be continued for an average period of 110.5 seconds.[21] The presence of oxygen, when not in excess, delays but does not entirely prevent the process of deoxidation.

Nitrogen is much less soluble in the blood than either nitrous oxide or oxygen, yet Dr. Hewitt has obtained, in my presence, distinct anæsthesia in two cases by administering a mixture of nitrogen with as much as 7 or 7½ per cent. of oxygen.[22] Since that proportion of oxygen does not prevent, though it delays, the anæsthetic action of nitrogen, it is quite intelligible that with a larger amount of oxygen the much more soluble nitrous oxide should be an efficient anæsthetic. This, however, requires further explanation.

But before entering upon this there is one important practical point relating to the action of nitrous oxide as an anæsthetic to which I am anxious to direct especial attention, and that is the manner in which the circulatory failure occurs. This failure is not the result of ordinary syncope, but, as numerous observations and experiments have shown, the immediate cause is the arrest of the pulmonary circulation and the consequent over-distension of the right side of

the heart. The remedy for this is the free access of air to the lungs, and in the almost infinitely small number of cases in which this fails the cautious inhalation of the vapour of nitrite of amyl, by relaxing the pulmonary arterioles, may succeed in overcoming the impediment. An experiment described in the earlier part of this paper affords a striking illustration of the influence of the vapour in removing the paralysing over-distension of the right side of the heart, even while nitrous oxide gas was still being thrown into the lungs. Another method of relieving the over-distension of the right side of the heart and so increasing its contractile power is to open the external jugular vein. Dr. John Reid in an interesting paper "On the Effects of Venesection in Removing and Increasing the Heart's Action under Certain Circumstances,"[23] has proved by numerous experiments on animals that when, as a result of apnœa, the heart has nearly or quite ceased to beat, its contraction may be renewed or invigorated by "disgorging the right side of the heart."

The Anæsthetic Action of Nitrogen.

It occurred to me, about four years ago, that some light might be thrown upon the anæsthetic action of nitrous oxide by observing the effect of inhaling nitrogen as nearly pure as it can be obtained. Accordingly I obtained from the Scotch and Irish Oxygen Company of Glasgow a metal cylinder containing 100 cubic feet of compressed nitrogen, in which the proportion of oxygen present was only 0.5 per cent., with 0.3 per cent. of carbonic acid. As a preliminary trial Mr. Woodhouse Braine did me the favour to administer this gas in five instances to members of the staff of King's College who volunteered to submit to the experiment. The result in each case was rapid and complete anæsthesia, with general phenomena precisely similar to those resulting from the inhalation of nitrous oxide; consciousness quickly returned when the facepiece was removed, and there were no unpleasant after-effects.

After this Mr. Braine felt justified in administering the gas as an anæsthetic to patients at the Dental Hospital. On the first occasion nine patients took the gas. In every case there was complete anæsthesia, with general phenomena precisely similar to those resulting from nitrous oxide inhalation. The pulse was first full and throbbing, then small and feeble. In the advanced stage there was cyanosis, the pupils were dilated, and there was more or less jactitation of the limbs. The only difference, in the opinion of some of those present, was that the anæsthesia was rather less rapidly produced and somewhat less durable than that from nitrous oxide, though in each case the tooth was extracted without pain.

On a subsequent occasion the gas from the same cylinder was administered by Dr. F. Hewitt at the Dental Hospital.[24] Nine patients took the gas, with results identical with those observed on the former occasion. Dr. Hewitt says "an onlooker could not have detected any difference between the phenomena produced and those usually met with under nitrous oxide." The maximum period of inhalation required to produce anæsthesia was 70 seconds, the minimum 50 seconds, and the mean 58.3 seconds.[25] In one case two teeth were extracted without pain. In only one case was pain ex-

perienced, and in that case, the tooth having been broken and not extracted, the patient said she felt "a smashing up."

Having on several occasions witnessed the administration by Dr. Hewitt of nitrous oxide mixed with about 10 per cent. of oxygen, I determined to try a mixture of nitrogen with a small proportion of oxygen. I therefore obtained from the company before mentioned a cylinder containing 40 cubic feet of nitrogen with 3 per cent. of oxygen, and a second cylinder of the same capacity containing nitrogen with 5 per cent. of oxygen. The 3 per cent. gas was given by Dr. Hewitt to five patients, and the 5 per cent. to four patients. With the 3 per cent. gas the time required to produce anæsthesia varied from 60 to 75 seconds, the mean time being 67.5 seconds. In each case the tooth was extracted without pain, the duration of the anæsthesia being somewhat longer than with nitrogen alone. In each case there was lividity, dilatation of the pupils, and more or less jactitation.

With the 5 per cent. gas the time required to produce anæsthesia ranged from 75 to 95 seconds, the average being 87.5 seconds. In each case the anæsthesia was complete, during which one patient had three molars extracted; and although she said she "felt the last two," the sensation appears to have been that of a mechanical pull and not acute pain. In all four of these cases there was slight lividity before the facepiece was removed, but in only one was there slight jactitation of the limbs. Dr. Hewitt, in describing the results of these experiments with mixed nitrogen and oxygen, mentions one fact which I had not noted, namely, that "there was some excitement after the inhalation in a few of the cases." Such excitement is not uncommon after nitrous oxide inhalation.

In undertaking these experiments with nitrogen, I had little expectation that it would ever come into use as a substitute for nitrous oxide; the practical impossibility of keeping the gas in a liquid form would alone forbid this, but it occurred to me that if the inhalation of a gas which could not be supposed to possess a specific anæsthetic property were found to induce insensibility of which an experienced anæsthetist might say "an onlooker could not have detected any difference between the phenomena produced and those usually met with under nitrous oxide," this would have gone far to prove that nitrous oxide, like nitrogen, produces anæsthesia by depriving the blood and the tissues of oxygen.

It is a confirmation of this view that a longer inhalation is required to produce anæsthesia when a small proportion of oxygen is mixed with either nitrous oxide or nitrogen, while as a result of this the available period of anæsthesia for operation is somewhat prolonged. The obvious explanation is that more of the gas is required to deoxidise the blood and the tissues when vitalising oxygen is mixed with an azotic gas, while a prolonged inhalation carries the process of deoxidation deeper into the fluids and tissues, and so lengthens the period of anæsthesia.

I learn from Dr. Hewitt that in giving nitrous oxide with oxygen he begins with two per cent. of oxygen and gradually increases it to about ten per cent. If nitrogen were given in the same manner and with the same proportion of oxygen the result would probably be identical.

If the late Dr. Snow had lived to see the general use of

nitrous oxide as an anæsthetic, he might have referred to it as affording additional evidence in support of his inference from numerous observations and experiments that "the action of the volatile narcotics is that of arresting or limiting those combinations between the oxygen of the arterial blood and the tissues of the body which are essential to sensation, volition, and all the animal functions."[26] He demonstrated that these substances modify, and in large quantities arrest, the animal functions in the same way and by the same power as that by which they modify and arrest combustion, the slow oxidation of phosphorus and other kinds of oxidation unconnected with the living body when these narcotics are mixed with the atmospheric air.

Previous Experiments with Nitrogen.

Until I read Dr. F. Hewitt's interesting book on *Anæsthetics*, I was not aware of the fact that about a quarter of a century ago Dr. Burdon Sanderson, Dr. John Murray, and Mr. Turner had administered nitrogen to six patients for tooth extraction at the Middlesex Hospital, the results of which are published.[27] The object of the experiment was to solve the question: "Does nitrous oxide act as an anæsthetic by excluding oxygen?" In the first two cases the inhalation was discontinued, as "the inhaler did not effectually exclude air." In the other four cases, "with a perfectly fitting inhaler," the results were as different from those which we obtained with nitrogen at the Dental Hospital as the authors rightly declare them to be from the action of nitrous oxide. Thus none of the patients showed any marked effects until the inhalation had been continued for two minutes, and for the production of insensibility the inhalation had to be continued for 3 min., 3 min. 10 sec., 4 min., and 4 min. respectively. There was no lividity, "a marked contrast" (as they say) "to the deep blue produced by nitrous oxide." In two of the cases extraction was perfectly painless, the other two said that although they had no pain they "felt it."

The report concludes by the statement that "the facts above related indicate that there is an essential difference in the mode of action of the two gases" namely, nitrogen and nitrous oxide.

What, then, is the explanation of the contrasted results of these experiments and of those above recorded as having been obtained at the Dental Hospital? The nitrogen may have contained a large admixture of oxygen, which would account for the length of time required to produce anæsthesia. If the gas was pure nitrogen it must have become largely mixed with air during the process of inhalation. Every anæsthetist knows how difficult it is, without a well-shaped and padded facepiece, to exclude air during the inhalation of any gas. It is certain, from our experience at the Dental Hospital, that no one could breathe pure nitrogen for even the shortest time mentioned in the Middlesex Hospital report. Even with a mixture of 5 per cent. of oxygen the longest period of inhalation required to produce unconsciousness at the Dental Hospital was 95 seconds.

It is not without interest to compare the results of the experiments at the Middlesex Hospital with those obtained by Sir Humphry Davy with nitrous oxide. The great chemist

would, no doubt, ensure the purity of the gas, but inhaling it, as he and others did, through a wooden tube held between the lips while the nostrils were closed, he could not exclude atmospheric air.[28] The result was, as he says, that he could breathe the gas for rather more than four minutes, but never so long as five.[29] It scarcely need be said that it is as impossible to inhale pure nitrous oxide for four minutes as it is to inhale pure nitrogen for that long period.

It is very noteworthy that when care is taken to exclude atmospheric air during the inhalation of the two gases—nitrous oxide and pure nitrogen—the average time required to produce anæsthesia is practically the same; so when the prolongation of the inhalation of nitrous oxide by Sir H. Davy and of nitrogen at the Middlesex affords conclusive proof that air or oxygen has not been excluded the increase of time required to produce anæsthesia was nearly equal in the two sets of cases. If Sir Humphry Davy could have inhaled, or seen others inhale, nitrous oxide unmixed with atmospheric air his account of the physiological effects would have been very different from that which he published at the beginning of the century, and the general use of the gas as an anæsthetic might not have been so long delayed.

I have proved that the inhalation of nitrogen, either pure or mixed with a small proportion of oxygen, rapidly causes anæsthesia not distinguishable from that which results from the inhalation of nitrous oxide. It now remains for anyone who still believes that azotic nitrous oxide, apart from its power of displacing the vitalising oxygen, exerts a specific anæsthetic influence to set forth the reasons for his belief; and in doing this he will, of course, bear in mind that it is worse than useless, it is seriously misleading to institute a comparison between nitrous oxide anæsthesia and the results of mechanical closure of the trachea.

The Theory of Choleraic Collapse.

The right interpretation of the phenomena of apnœa, whether a result of the mechanical exclusion of air from the lungs or of the inspiration of an azotic gas, such as nitrous oxide or nitrogen, affords much assistance towards the solution of some most interesting and important pathological problems, and amongst these the pathology of the collapse stage of cholera is by far the most interesting. The condition of the heart's cavities which I have before described as occurring in the final stage of apnœa is identical with that which is found after death in the collapse stage of cholera.

We are indebted to the late Dr. Edmund Parkes[30] for the first accurate description of the condition of the heart and lungs after death in the stage of collapse. The following is a brief summary of the appearances, which he describes at great length. "The right side of the heart and the pulmonary arteries were generally filled, and in some cases distended with blood; the left side and the aorta were generally empty or contained only a small quantity of dark blood. The inference that was drawn from the state of the cavities in the greater number of cases was that the right side had continued to receive blood till, in some cases, it became full and even distended, while the left side received little or no blood, but had continued to contract upon the last drop of blood

which had entered it.....In the lungs there was a remarkable want of air (that is, after the chest was opened); in the most rapid cases a want also of blood in the minute texture, causing the lung to collapse when the chest is opened and its weight to be diminished in a very great degree.....The conditions of the heart and lungs seem to point out unequivocally that in cholera the blood does not pass (freely) through the lungs." The only explanation of the condition which Dr. Parkes could suggest was that "some change in the fibrine" of the blood caused an impediment or arrest in the pulmonary capillaries (p. 113).

Dr. Parkes's book was published in 1847, some years therefore before the researches of Bernard, Brown-Séquard, and others had made known the function of the vasomotor nerves and the arterioles.

In a book on *Epidemic Diarrhœa and Cholera* which I published in 1855, I expressed my belief that the arrest of the pulmonary circulation is a result of contraction of the arterioles excited by the poisoned blood, and I adduced many facts and arguments in support of that theory. The condition of the heart and lungs is identical with that after death by apnœa, the difference in the order of events being this, that in cholera there is a primary asphyxia, that is, an arrest of the blood before it has reached the pulmonary capillaries, and a secondary apnœa, the result of the blood not being brought into contact with the air in the cells of the lung; on the other hand, when death is caused by privation of air there is a primary apnœa. The blood which enters the capillaries not meeting with atmospheric air in the pulmonary cells, asphyxia—arrested circulation—is a secondary result. The term "cholera asphyxia" therefore, which was used by Scot, Bell, and other writers in India, was more strictly accurate than its authors were aware of. They no doubt meant to convey the idea that cholera was a suffocative disease, but the physiology of their time would not enable them to see the precise manner in which the aëration of the blood was prevented.

That Dr. Parkes was ready to accept my explanation of the phenomena which he was the first to describe appears from the following sentences in a letter which I received from him in November, 1865. He had been reading some papers of mine which were published the British Medical Journal, and he wrote: "I feel pretty sure that you are right in attaching great importance to the difficulty of passage of blood through the lungs, which I always fancied depended on some condition of the blood itself, but I see that you attribute great effect to contraction of the arteries. This is certainly a very important point to work out, and seems to have evidence in its favour, at any rate that it is a co-operating cause. From what I have seen of your papers it seems to me that they will be a very important addition to our knowledge of cholera."

The pathology of cholera is too large a subject to be treated in detail in this paper. In the chapter "On the Pathology and Treatment of Cholera," in my *Medical Lectures and Essays*, the whole subject is fully discussed, and all reasonable and unreasonable objections to my doctrines have been, I venture to say, fairly met and refuted. In that chapter (p. 124) I have referred to the effect of the subcutaneous injection of

the sulphate of atropine in doses of from $\frac{1}{60}$ to $\frac{1}{30}$ of a grain, as described by Dr. Saunders in the *American Practitioner* (July, 1873). "In some cases the relief afforded was astonishing; the skin grew warm, the pulse rose, the surface previously shrivelled and clammy assumed its natural condition, and in some instances the patient slept soundly for several hours." The explanation is to be found in the removal of the impediment to the pulmonary circulation by the paralysing effect of the atropine on the arterioles. In the same chapter I have shown that the marvellous temporary effect of a hot saline injection into a vein is to be explained partly by the dilution of the poisoned blood, but mainly by the high temperature of the injected liquor causing relaxation of the pulmonary arterioles. The cases recorded by Indian practitioners, in which patients in a state of almost pulseless collapse have obtained astonishing relief by venesection, are explicable by the disgorgement of the over-distended right cavities of the heart. The condition of the heart's cavities is the same as in the final stage of apnœa, in which, as we have before seen, venesection increases the contractile power of the heart, or even restores its contractions after they have ceased.

The time is not far distant when it will be universally acknowledged that the hypothesis which attributes the collapse stage of cholera to the drain of liquid from the blood (the dehydration theory) is inconsistent with the facts, while in its application to practice it has been one of the most disastrous that ever gained general acceptance.

Variations of the Pulse; and the Cardio-vascular Changes in Bright's Disease.

The two physical forces upon which mainly depend the volume and strength of the pulse are the contraction of the left ventricle at one extremity and that of the arterioles at the other. But another important factor is that of the volume of blood in the systemic arteries. For instance, the small and feeble pulse during the collapse stage of cholera is a result of the scanty stream of blood which passes through the lungs to the left side of the heart, the ventricle being also weakened by the defective supply of blood to the coronary arteries. The rapid changes in the character of the pulse during the successive stages of the various forms of apnœa I have already described and explained.

When, as a result of disease of the respiratory organs, imperfectly aërated blood enters the systemic arteries, an unwary practitioner may misinterpret the full and strong pulse as a favourable sign, whereas it is a result of increasing deoxydation of the blood.

Very valuable information may be obtained from an intelligent observation of the pulse in the various forms and stages of Bright's disease. In cases of acute nephritis with a scanty secretion of urine and consequent uræmia, the pulse is usually full and tense, a result of contraction of the systemic arterioles excited by the impure blood. The fulness and tension pass away when the excretory function of the kidneys has been restored.

The long-continued uræmia which results from chronic degeneration of the kidneys, and especially from the con-

tracted granular kidney, is associated with very remarkable changes in the circulatory system. The radial pulse is very full and tense, the large arteries are thickened and tortuous, and there are the physical signs of hypertrophy of the left ventricle of the heart. Some years since I was led to search for the cause of this condition by the following considerations: Hypertrophy of the left ventricle without disease of the valves or of the large arteries—a fact made known by Dr. Bright in the first volume of the *Guy's Hospital Reports*—is probably a result, as he suggested, of some impediment "in the minute subdivisions of the vasçular system." Reasoning from analogy, I thought it probable that the impediment is caused by the contraction of the arterioles excited by the impure blood, and further, that their long-continued overaction would result in hypertrophy of their walls, corresponding with the hypertrophy of the left ventricle. This led me to search for and to find the hypertrophy which I had anticipated in the arterioles of every tissue that I examined—in the kidneys, intestines, skin, muscles, and pia mater. The prolonged overaction of the arterioles registers itself in a conspicuous hypertrophy of their muscular walls.[31]

No kymograph could afford a more certain indication of excessive contraction of the arterioles, with resulting high arterial tension.

My description of the thickened arterioles, after passing through the inevitable ordeal of misrepresentation and ridicule, is now admitted to have been correct. The change in question is an example of true hypertrophy—overgrowth of a tissue without change of texture—not to be confounded with lardaceous degeneration, the irregular thickening which results from any form of arteritis, or the so-called "hyalin-fibroid change." The tortuosity and thickening of the larger arteries in the advanced stage of chronic renal disease are results of the excessive strain to which they are subjected between the hypertrophied left ventricle and the resisting arterioles.

The coexistence of cardiac hypertrophy with high arterial tension is very significant of renal degeneration in an advanced stage.

Some writers appear to assume that high arterial tension implies an increase of pressure within the capillaries, but this is an erroneous assumption. In fact it is obvious that if the increased resistance caused by the contracting arterioles be not compensated by increased propulsion from the heart, the intracapillary pressure would be diminished, but it is probable that the opposing forces are so nicely balanced that the pressure in the capillaries is, in most cases, unchanged.

Raynaud's Disease.

A remarkable form of arrested circulation, which was originally described by Dr. Maurice Raynaud in his treatise *De l'Asphyxie locale et de la Gangrène symétrique des Extrémités* (Paris, 1862) is, by general consent, attributed to excessive contraction of systemic arterioles in localised regions. Raynaud's original treatise and his later researches, which were published in the *Archives générales de Médecine*, 1874,

vol. i, have been translated by Dr. Thomas Barlow. This translation, together with a valuable appendix by the translator, forms part of a volume of selected monographs which was published in 1888 by the New Sydenham Society. Referring to that volume for the detailed history of this remarkable affection, I can now do no more than indicate very briefly its general characters.

The essential features of Raynaud's disease consist in a local arrest of the circulation, with consequent coldness, blueness, and often dry gangrene of extreme parts, such as the fingers, the toes, the tip of the nose, and the ears. There is also a remarkable tendency to symmetry in the parts affected, so that the disease usually, though not quite constantly, implicates corresponding parts on the two sides. Thus the upper or lower limbs, or all four together, may be bilaterally affected. In some cases the local gangrene is associated with that form of recurring hæmaturia which is called intermittent hæmoglobinuria.

This affection differs from senile gangrene in the fact that there is no structural change discoverable in the walls of the arteries, and in a large proportion of cases the patients are below 30 years of age.

Referring to M. Claude Bernard's researches into the action of the muscular-walled arterioles, Dr. Raynaud says: "The physiology of the circulation has been enriched in late years by one of the most beautiful discoveries of the century." Yet, with a confusing inaccuracy of language, he occasionally speaks of contraction of the capillaries, when from the context it is evident that he is referring to the arterioles. I venture also to criticise his use of the terms "local syncope" and "local asphyxia." The arrested circulation, he says, "can be compared to nothing better than syncope, in which the action of the heart is momentarily suspended" (p. 30). But, surely, to compare the failure of circulation resulting from suspension of the action of the heart with an arrest which is acknowledged to be caused by arterial contraction is to confound phenomena which are essentially different. The proper term by which to designate the arrested circulation in Raynaud's disease is local asphyxia, a result of arterial contraction. Raynaud, however, referring to the presence of unoxygenised venous blood in the implicated tissues, calls this "local asphyxia." The correct term is local apnœa.

The word "asphyxia" has become so closely associated in men's minds with the idea of suffocation that, in spite of its obvious etymological meaning, it is frequently misapplied even in scientific treatises. This misapplication has the further disadvantage of leaving no term by which to distinguish an arrest of the circulation and of the pulse from apnœa (suffocation).

I hope to have established my position that the influence of the vasomotor nerves and the arterioles forms a connecting link between the diverse pathological conditions which are the subject of this communication, but there are many other clinical and pathological facts to the interpretation of which a similar influence is believed to be more or less applicable. M. Vulpian,[32] in the second volume of his work before referred to, has given an admirable summary of many pathological conditions, apparently associated with vasomotor nervous influence.

NOTES AND REFERENCES.

[1] *Wochenschrift für die gesammte Heilkunde*, 1840, No. 21. [2] *Comptes Rendus*, March 29th, 1852. [3] The function of respiration requires a free access of air to the pulmonary cells and of blood to the capillaries. The exclusion of the former is apnœa, of the latter asphyxia. [4] *Physiological, Anatomical, and Pathological Researches.* [5] *Edin. Med. and Surg. Journal*, 1845. [6] It has been ascertained that the vasomotor centre in the medulla is not the only one, but that there are others along the whole length of the spinal cord and in the ganglia of the sympathetic, which, after section of the cord, may act as centres for the vasomotor fibres in parts below the division of the cord. See Dr. M. Foster's *Textbook of Physiology*, 5th edition, p. 329; Cohnheim's *Lectures on General Pathology*, New Sydenham Society's translation, vol. i, p. 113; and Vulpian's *Leçons sur l'Appareil Vasomoteur*, Tome I, p. 284. [7] *Op. cit.*, p. 608. [8] *Philosophical Transactions*, 1867; *Proc. Roy. Soc.*, 1867. [9] One of the aliases for curara or curare. [10] *Proc. Roy. Soc.*, 1867, p. 393. [11] For an account of the influence of Professor Sanderson's teaching upon subsequent writers on the physiology of asphyxia see my *Essay on Asphyxia (Apnœa)*. [12] When the chest of an animal is opened immediately after death caused by a sudden deprivation of air the proportion of blood on the right and left side of the heart respectively is about that of 8 to 1, or ounces to drachms. After a prolonged and complicated experiment ending in apnœa, the heart's walls and the arterioles are enfeebled, and the disproportion of blood on the two sides is consequently less. Care must be taken to avoid wounding a large vein in opening the chest. Such a wound would quickly reduce the amount of blood in the right side of the heart, and the previously distended cavities would be found nearly empty. [13] *Lancet*, February 17th, 1872, p. 213. [14] It has been shown in Ludwig's laboratory that the arteries of an organ that has been withdrawn from all nervous influence contract when venous blood flows through them. Cohnheim, *Op. cit.*, p. 112. [15] The difference between ordinary venous blood and the blood in the veins and the right side of the heart after death from apnœa is that the former contains some oxyhæmoglobin, as shown by the spectroscope, while the latter contains none. [16] *Op. cit.*, p. 626. [17] *Proc. Roy. Soc.*, vol. xlv, p. 369. [18] See Kussmaul and Tenner on Epileptic Convulsions from Hæmorrhage, New Sydenham Society's collected *Monographs*, 1859, and the Pathology and Treatment of Epilepsy in my *Medical Lectures and Essays*, p. 236; [19] *Anæsthetics and their Administration*, p. 114. [20] *Op. cit.*, p. 106. [21] *Op. cit.*, p. 130. [22] *Op. cit.*, p. 269. [23] *Op. cit.*, p. 51. [24] See Dr. Hewitt's account of this administration. *Op. cit.*, p. 268. [25] Dr. Hewitt (*op. cit.*, p. 106) gives the maximum time of inhalation of nitrous oxide in 40 cases as 70 secs., the minimum 25 secs., and the average 51 secs. [26] See the *Life of John Snow, M.D.*, by Sir Benjamin W. Richardson, M.D., F.R S., introductory to Dr. Snow's work on *Chloroform and Other Anæsthetics*, p. xiv. Also my lecture on the Pathology of Coma and Anæsthesia, *Medical Lectures and Essays*, p. 290. [27] BRITISH MEDICAL JOURNAL, 1868, i, p. 593. [28] In cases where the form of the mouth prevented the lips from being accurately closed on the breathing tube he used a tin plate conical mouthpiece fixed to the cheeks and accurately adapted to the lips. It would be scarcely possible to make such an arrangement airtight. [29] *Collected Works*, vol. iii. p. 273. [30] *On Asiatic or Algide Cholera.* [31] See *Med. Chir. Trans.*, vol li; and *Medical Lectures and Essays*, p. 694. [32] *Leçons sur l'Appareil Vasomoteur.*