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RECENT ADVANCES IN ANAESTHESIA WITH SPECIAL REFERENCE TO RESPIRATORY PHYSIOLOGY

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> "It was not the subsiding or movelessness of the lungs that was the immediate cause of death, or the stopping of the circulation of the blood through the lungs, but the *want* of a sufficient *supply of fresh air.*" — ROBERT HOOKE (1)

Thus spoke Robert Hooke before the Royal Society in 1667, and Sir William Bayliss (2) gives him eulogy for showing "at one meeting a dog, which was kept alive, after removal of the ribs and the diaphragm, by blowing air into the windpipe with bellows. The absence of convulsions was noted. These made their appearance when the supply of air was stopped, but were put an end to by renewing the blowing of air". The fundamental discoveries of this contemporary of Boyle, Leibnitz and Newton were soon followed by those of John Mayow in 1674 (2), when, from his experiments, he showed that with respect "to the use of respiration, it may be affirmed that an aerial something *(spiritus nitro-aereus)*, whatever it may be, essential to life, passes into the mass of the blood. And thus air driven out of the lungs, these vital particles having been drained from it, is no longer fit for breathing again." This aerial something is what we now call oxygen. These vital particles call to mind "the most brilliant, and the most fruitful, of all scientific hypothesis", namely, the atomic theory invented by Leucippus, worked out by Democritus, taught by Epicurus and poetized by Lucretius in his *de rerum natura*. They called these particles *corpora prima*, or atoms: (3)

> . . . . , et aer,
> scilicet ut debet qui semper mobilis extat,
> per patefacta venit penetratque foramina largus
> et dispargitur ad partis ita quasque minutas 895
> corporis.
>
> *de rerum natura, IV*

Translation:

> . . . . , and the air
> (as you might expect with something always so sensitive
> to movement) passes and penetrates through the opened
> passages in abundance, and so is distributed abroad
> into the very smallest parts of the body.

We do not intend to dwell on the history of respiratory physiology, but always we shall revere the memory of Priestley, who "rediscovered" oxygen on the first of August, 1774, and later became such a leading Jeffersonian that Jefferson himself "relied heavily on his advice..." (4) We shall always revere the memory of Lavoisier (5), *le fondateur de la chimie moderne,* who, shortly after the days of Voltaire and Rousseau, established the fact that oxygen was the universal oxidizing principle. The late Professor Graham Lusk, in his text-book, *The Science of Nutrition,* continually expressed amazement at the penetration of Lavoisier's experiments and stated that "these remarkable results are in strict accord with the knowledge of our own day. We know more details, but the fundamental fact that the quantity of oxygen absorbed and of carbon dioxide excreted depends primarily on a) food, b) work, and c) temperature, was established by Lavoisier within a few years after his discovery that oxygen supported combustion." Lusk goes on to state: "The modern era of the science of nutrition was opened by Lavoisier in 1780. He was the first to apply the balance and the thermometer to the phenomenon of life, and he declared *La vie est une fonction chimique.*" (One does well to consult Kerr's translation of Lavoisier's *Traité Élémentaire de Chimie*) (6). Barron (7), too, gives similar support and declares that foodstuffs "are oxidized in living cells at relatively low temperatures, at neutrality, through the action of mild oxidizing agents, the oxidizing enzymes. Thus cellular respiration, the consumption of oxygen accompanied by the production of carbon dioxide and water, represents the integral of a numeber of partial oxidation-reductions, each of which has its peculiar mechanism."

Although it is true that deference must be paid to the distinctions customarily made between *external* respiration and *internal* respiration, yet we do not intend to dwell upon them for the simple reason that the activities involved do overlap and become interwoven, in manner seemingly "mysterious", at least at the alveolar border. Besides, we feel that ordinarily not nearly enough emphasis is given to the great importance of interdependence of function (8). As examples, it ought to be kept in mind, and stressed continually, that the many vital functions of the liver would not get very far without pulmonary ventilation and the circulation of the blood; and it ought always to be remembered that circulatory and respiratory systems function in harmony under similar influences at and from their respective centres and outlying chemoceptors. How pervadingly intertwined and abundant is function between the nervous system, the circulation and respiration, and too, the organs generally. "To consider any one without the other is to be blind and halting." (8)

In recent times, the most generally well-accepted teaching concerning the respiratory centre is that which comes from the department of physiology of Cornell University. Pitts and his co-workers emphasize "the anatomical distinction of the inspiratory and expiratory centres, and the lack of inherent rhythmicity of the medullary centre. According to Pitts, rhythmicity is imposed on the medullary cells by the vagal stretch reflexes and the pontine pneumotaxic centre." (9) Pitts states that "the neurons of the respiratory centre are sensitive to the chemical and physical constitution of fluid environment. They are excited by impulses impinging upon them by way of collaterals of the major sensory and motor tracts. Under combined chemical and synaptic stimulation these neurons discharge impulses repetitively... In the absence of inhibitory influences which act upon the inspiratory centre from without, its discharge is continuous, and maintained tonic inspiration or apneusis results... The rhythm of breathing is impressed upon the respiratory centre by inhibitory mechanisms operating from without; it is not an expression of properties inherent in the neurons of the centre. The depth of breathing is determined by the sensitivity of these neurons to their environment and by the excitatory influences exerted by the many afferents which impinge upon them." (10)

This hypothesis, boldly challenging the classical doctrine of innate respiratory periodicity, was the outcome of some brilliant sets of work. However, in complete antithesis, there has appeared, just lately (Aug. '49) from the department of physiology of Baylor University, a report of many experiments the results of which strengthen the older view. Indeed, Hoff and Breckenridge (11) give the following summary: "Apneusis in the dog is neither permanent nor total nor an invariable consequence of low decerebration and vagotomy. The denervated medullary preparation is capable of normal periodic respiration. Apneusis represents a phenomenon superimposed upon the basic medullary activity. The medullary respiratory centre is inherently periodic." Here we have before us two findings diametrically opposed to one another, each coming from heads and hands, equally competent and equally capable. Which are we to accept ? — which teach ? On reflection, it may appear that they are not so very much at variance, indeed, they may turn out to be quite complementary. One fact that does come to mind is that the two sets of experiments were done on different kinds of animals, the one on cats and the other on dogs. The difference may be entirely one of species. If this be so, then, in terms of human physiology, one might be justified in leaning towards the results which were obtained from the work on dogs, that is, from an evolutionary point of view.

Be all this as it may, one cannot help but be facinated and give great credit to the observers of both sides. Let us gladden our hearts that we have new light thrown upon the all — important problem concerning the constant hovering of air at such close propinquity to blood that there is a continuous give-and-take of gases through the alveolar wall; not unlike the brooding of the air over the waters, and one remembers that Macallum (12) gave evidence in 1903 that the blood plasma with a closed circulatory system is, in its inorganic salts, but a reproduction of the sea water of the remote geological period in which the prototypic representatives of vertebrates first made their appearance, verily, we have within us "an heirloom of life in the primeval ocean.

It seems fair to say that by how much the more anaesthesia is developed by so much the more will the scope of laboratory investigation be increased, and still further, so much the more will the arm of surgery be extended in humane rescue. With this in mind, properly to consider the topic of recent advances in anaesthesia is to cause us not only to take stock of how we stand but also to make plans for the future. Latterly a widespread interest in the provision of opportunity to learn anaesthesia has been more fully realized and, already, at a number of universities, departments of anaesthesia have been established. We are convinced that this constitutes the best of the recent advances in anaesthesia. During 1948 and 1949 there were several articles advocating improvement in the teaching of anaesthesia not only to the undergraduate but also to the graduate of medicine (13, 14, 15 & 16), and it is encouraging to know that medical schools are paying more and more attention to the necessity. "Now and again the good news comes of the setting up of yet another department of anaesthesia at some hospital or university, or both; in either instance additional timeliness is offered those who desire to learn anaesthesia." (13)

One of these several articles was written by Dripps (16). It is excellent. The following are some of the pithy statements he makes: "During the past decade medical research has attracted more workers, cost more money, aroused more interest and led to the publication of more articles than at any other time in history." "The first change is essentially a shift from the study of animals to the use of man as the experimental subject. It is axiomatic that a laboratory worker must warn against the hazards of transferring directly to man measurements obtained on animals. Species difference has been an obstacle which has had to be faced by every investigator studying the guinea pig, mouse, cat or dog." "This shift in emphasis towards clinical investigation has been made possible in part because of the development of new instruments and new technics for recording experimental data." "For the investigator of the human circulation there are methods available which measure cardiac output, direct arterial and venous pressures and pressure pulse waves, and blood flow in a variety of tissues and organs." Then he mentions several methods and goes on: "Using the technics just described, a clinical investigator can obtain information of great value to the anesthesiologist. For example, he can study the circulatory changes associated with spinal anesthesia. He can analyze circulatory abnormalities related to posture, to the surgical manipulation of viscera, the application of positive pressures in the respiratory tract and the use of various drugs. Results of such studies will inevitably make the practice of anesthesiology safer, more rational and more accurate." "The nitrogen analyzer of Lilly and Harvey permits an estimation of the uniformity of alveolar ventilation in a fraction of a minute (17). The diffusion of gases across the alveolar-capillary membrane can now be studied more accurately. Pulmonary blood flow can be measured. Finally, not only can one study the lung as a whole but, with the technic of bronchospirometry, one can estimate the contribution which each lung is making to the total. This may be of assistance to the anesthetist and the thoracic surgeon attempting to decide whether a particular patient has sufficient pulmonary reserve to withstand pneumonectomy or lobectomy." Dripps recommends that hospitals should have "Clinico-physiologic Conferences" to be attended by biochemists, physiologists, pharmacologists, bacteriologists and others directly associated with the preclinical sciences, along with clinicians, so to have common discussion of a patient's problems as they are presented in the hospital wards, so to bridge the gaps in knowledge which exist in clinical medicine. If Herbert Spencer (18) could realize "the increasing inter-dependence of the sciences" in 1854, how much more ought it to be impressed upon us now-a-days ?

All this is illustrative of how one may learn anaesthesia to best advantage, not only by itself but in an interrelated manner, so to circumvent the narrowness which has accrued with the ever growing number of specialisms, so to comply with the counsel of Comte (19). Remember he said, in 1830, that as long as we have a class of learned men to connect each new discovery with the general system, we need not have fear of losing sight of the great whole on account of pursuing the details; on the contrary its development will extend and not change in character. Let us take note, too, that just lately, four distinguished educationalists from the Bell Telephone Laboratories and the Universities of Harvard, Princeton and Johns Hopkins have expounded their views on *The Education of a Scientific Generalist* (20). They summarize thus: "Science is complex; yet it must become manageable. It can be managed better with the help of a few scientists with training in many sciences. A few such scientific generalists can be trained tomorrow with the courses at hand. To make science more manageable, we must perform a new and difficult synthesis on a higher level of organization." All this is illustrative and suggestive of method. Seeing that there is such a grievous dearth of trained professional anaesthetists, it becomes the duty of those in authority at the medical school to provide opportunity. All this is united, in thought at least, with *the best of the recent advances* in anaesthesia. Let us ponder the words of Charles Eliot Norton, from a letter he wrote to John Ruskin in July 1871 about Tintoret; "But considering that he painted more than all the other Venetian masters of his day put together, that he was never idle, that his imagination was never in repose, it is astonishing that he did so little that is trivial, or that bears signs of weariness or exhaustion." (21)

Recent advances in anaesthesia, from the clinical point of view, have been so many that only a few will be dealt with at this time. At a meeting of the Quebec Division of Canadian Anaesthetists' Society Charles L. Burstein (22) presented data concerning reflex cardiocirculatory disturbances during such intrathoracic operations as: pneumonectomy, lobectomy, pericardiectomy, transthoracic vagotomy, transthoracic gastrectomy, operation for mediastinal tumor and thoracotomy. In order to obviate the fall in blood pressure which follows the change of position from supine to lateral, it is recommended to "place the patient in the operative position from the outset" and to induce anaesthesia and perform tracheal intubation in that position. Cardiac irregularities of a reflex nature occur frequently at the moment of intubation. This is less likely in deeper anaesthesia. Periosteal rib scraping and wide rib spreading may cause cardiovascular changes characterized by A-V conduction defect, nodal rhythm, and arterial hypotension. An effective way of preventing these abnormalities is by injecting the intercostal nerves with an anaesthetic solution. The arterial hypotension and bradycardia due to vagal stimulation from manipulation of the hilar pulmonary plexus or from direct mechanical pressure upon the vagus nerve can be abolished by infiltration anaesthesia. Cardiocirculatory reactions from manipulation or incision of the pericardium can be prevented by procaine topically and intravenously.

At this juncture it seems apposite to say something about the choice of anaesthetics in the hospitals associated with McGill University. To begin with, we believe that it matters not so much what drugs and what methods are used but more particularly it is of prime importance that the anaesthetist should be so familiar with these that he can choose freely from among them, without prejudice, solely in the interest of the patient. "The best choice is made when the physician, the surgeon and the anaesthetist discuss the general physiological state of the patient, as well as the surgical requiremens of the case. The physician's opinion, the views of the patient's doctor, are of inestimable value for the particular reason that he knows his patient, he knows something of the episodes in the life of the individual, some of which may be of a psychological nature. He helps profoundly to decide the procedure. With polarity of mind these three medical philosophers, after considering the nature of the operation that must be done and the character of any additional disability, will choose the drugs to be used and the manner of their employment, while being fully aware of the harmful effects which they are capable of producing. After decisions is made the duties become, in effect, esoteric to the anaesthetist — they are essentially his responsibility." (23)

Here are a few examples of choice: (24)

1. *Thoracoplasty:*

First stage: Spinal anaesthesia with 1:1500 nupercaine according to modifications of the Etherington-Wilson technique.

Second stage: May be maintained by any one of three methods.

a) Intravenous injection of pentothal combined with endotracheal administration of nitrous oxide and oxygen.

b) Intravenous injection of pentothal and of curare, combined with endotracheal administration of nitrous oxide and oxygen.

c) Endotracheal administration of cyclopropane.

Third stage: A combination of paravertebral and field block anaesthesias.

2. *Surgery of the Lungs:*

Dry cases: Spinal anaesthesia with 1:1500 nupercaine, orotracheal administration of oxygen and intermittent intravenous injection of procaine, and postoperative bronchoscopic suction. Cases with excessive sputum. Two methods may be employed. a) Endotracheal administration of cyclopropane with postural drainage and intermittent suction, and intermittent intravenous procaine. b) Intravenous injection of pentothal, and of curare, combined with administration of nitrous oxide and oxygen.

In all of these cases, as faithfully as is oxygen given, so too are continuous blood transfusions given.

In operations on the lung or heart in children, where perforce the thorax must be open and exposed to atmospheric pressure, normal respiratory function is altered. Not only are the dynamics of respiration disturbed, but the surgeon must plunge his scalpel into organs most vital to the very existence of the patient. Under such circumstances it becomes mandatory for the anaesthetist to recognize certain basic physiological principles which must be adhered to as minutely as possible during the course of the operative manoeuvre. Even small deviations from the normal will pyramid themselves and create abnormalities which are prejudicial to the safe recovery of the patient.

The factors concerned in normal physiological function are simple to enumerate, but frequently difficult to achieve and maintain in small children undergoing major thoracic interventions. The primary one of adequate oxygenation of the arterial blood, and hence of the vital cerebral centres, exposes a problem concerning which some progress is being made. By means of tiny photo-electric cells which translate minute colour changes of the ear into objective numerical records, instantaneous knowledge is at hand of the changing arterial oxygen saturations. The oximeter will indicate a falling arterial oxygen tension long before such changes may be suspected by the clinician. The advantage to the anaesthetist of such an apparatus is almost unprecedented.

Not only must the patient receive adequate oxygen, but his carbon dioxide must be eliminated completely. A gaseous acidosis must not be superimposed on an altered respiratory function. Proper execution of this requirement demands not only good alveolar exchange, but also proper means of reducing dead space to a minimum. Furthermore, the provision of a foolproof method casting out from the anaesthetic circuit this gaseous product of metabolism, either by soda-lime absorption or by means of a non-rebreathing valve must not be forgotten.

An important principle not to be ignored in children relates to the fatigue engendered by long operative procedures. This may be lessened, and energy stored up for the convalescence, by reducing to a minimum the resistance against which the patient must breathe in the anaesthetic circuit, and by manually assisting his respiratory movements during operation.

Finally, the manipulations and assistance of the anaesthetist must not act to diminish the return flow of venous blood to the heart. By virtue of the surgical interference, the thoracic pump is already dislocated, and it would be foolhardy to disturb such altered physiology to a greater degree.

How best may one proceed to maintain these physiological functions within normal limits during thoracic surgery ? In the presence of the altered mechanics, and when subjected to the influence of depressent anaesthetic agents, spontaneous respirations are not sufficient. For gaseous exchange to be adequate at the àlveolar surfaces, the anaesthetist must assist the expansion and deflation of the lungs. It has been shown experimentally in dogs that the most advantageous method of accomplishing this assistance to respiration is by the alternate imposition of negative and positive pressures to the trachea and bronchi. This "suck and blow" concept, which appears to disturb least the physiological balance, is receiving clinical trial at this moment.

Methods of increasing respiratory exchange which are commonly employed in the operating room today include respiration which is completely controlled by the anaesthetist, or that in which the inspiratory phase is aided or "compensated" (25) by the anaesthetist, while the expiratory phase is spontaneous. These techniques provide adequate exchange, but may tend to lessen the venous return to the right side of the heart. "Positive pressure breathing" (26), during which the pressure within the lungs is higher than that of the atmosphere at all phases of the respiratory cycle, definitely interferes with blood return to the heart, and should never be condoned for periods longer than five minutes.

Anaesthetic apparatus and agents employed for paediatric thoracic surgery should be tailored to suit the required physiological demands. Of least importance is the agent selected, be it cyclopropane, ether, pentothal, or nitrous oxide and curare. Any one or combination of these may be feasible, provided the technique and manner of administration does not work against the physiological requirements of the patient. In infants under two years of age, employment of a non-rebreathing valve with "compensated" respirations appears to work best towards the desired principles (27). In older children similar assisted respirations may be utilized with the to-and-fro carbon dioxide absorption technique. Canisters should approximate the tidal volume of the patient, and should be changed frequently to avoid accumulation of carbon dioxide in the circuit. But no matter what the agent or technique a satisfactory outcome will depend on the acumen, diligence and application of knowledge on the part of the doctor "at the head of the table" (28).

Since the first use of curare in anaesthesia by Griffith (29), in 1942, a number of variants or substitutes have been proposed. The most promising of these are decamenthonium, flaxedil and metubine. In a recent review it has been pointed out that "the comparative clinical study of closely similar drugs is extremely difficult. Controlled statistical studies in an enormous number of cases should be done before anyone has the right to state dogmatically that decamethonium, flaxedil, metubine or anything else is better or safer than d-tubocurarine chloride. A synthetic product, it is true, may have advantages over natural curare from the point of view of availability and cost of manufacture, but in the interest of our patients we should not lightly abandon the d-tubocurarine preparations presently in use until at least comparable clinical safety has been established for the new products." (30) However, "a new chapter has been added to the story of anaesthesia by the introduction of muscle relaxants." "We will always have available for use some safe relaxing drug, whether of synthetic or natural origin."

Another use for curare has been brought to light by Burstein, Jackson and Rovenstine (31). Certain autonomic reflexes — celiac plexus, carotid sinus and vagal — may be abolished or alleviated by the administration of a dose of d-tubocurarine sufficient to produce intercostal paralysis. The fall in blood pressure, the diminution in pulse pressure and the bradicardia which may result from disturbances of these reflexes can be prevented by this drug.

It is realized that there are several other recent advances in anaesthesia, such as the many-sided studies on *Diffusion Respiration* (32) and those which belong to the coherent science of Enzymology wherein, as we consider that each cell contains an array of enzymes which operate side by side and in close coördination, simultaneously building up and breaking down dozens of complex products of metabolism, we can appreciate the delicacy of the equilibrium within the cell and the complex physiological equilibrium between all the cells of the body. Too few of us appreciate how sensitive the cellular enzymes are to disturbances in the composition of the cellular fluid. Very slight changes in the content of water, electrolyte, or metabolites, or the presence of foreign substances may seriously disturb the cellular enzymes. The action of drugs and the phenomenon of poisoning are simple manifestations of the interference with normal enzyme activity When the disturbance becomes severe or prolonged, the damage may be irreparable. The recovery of the patient depends on the restoration of the normal chemical composition of the cell fluids and the recovery of normal enzyme function. (28)

Finally, it is felt that these considerations may suffice to stimulate within us an abhorrance for complacency, an ardour for higher perfection, and a living urge towards inquiry. Let us remind ourselves, with Alfred North Whitehead, "that no static maintenance of perfection is possible. This axiom is rooted in the nature of things. Advance or Decadence are the only choices offered to mankind." (33)

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