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RECENT DEVELOPMENTS IN RESPIRATORY PHYSIOLOGY RELATED TO ANESTHESIA * †

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IN a previous contribution to this journal (1) attention was invited to a reinterpretation of long-familiar observations in the field of respiratory physiology and pharmacology, leading to the conclusion that nearly all of the important adjustments of respiration to changing conditions depend more on reflexes to the respiratory center than on chemical stimuli acting directly upon it. Another way of stating the same view is that changes in the chemical stimulus in the blood under ordinary physiologic as well as most pathologic conditions are results rather than causes of changes in pulmonary ventilation (13). The phrase "revolution in respiratory physiology" is true in both senses of the term revolution, for the earliest modern conceptions of respiratory control, advanced just a century ago, placed the main emphasis on reflexes (2, 3) and the wheel has now described a full cycle. There is this difference, however, that whereas in 1844 nobody suspected the complexities that underlie the functions of the central nervous system and therefore everybody could indulge in very simple explanations, that is certainly not the case now. Another difference is that in 1844 there was no particular immediate urgency about problems of respiratory physiology, but in modern mechanized war, in which man is the limiting factor in the performance of such vehicles as airplanes, tanks, and submarines, the identification of these weaknesses and the provision of means for overcoming them has become one of the major tasks of physiologic research (4). Many of these weaknesses lie in the respiratory system, and the "revolution in respiratory physiology" has therefore gained momentum.

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The critical reexamination of ideas long held has been extended to numerical constants that had long been accepted, as well as to explanations that had been firmly established. I have chosen, more or less at random, four examples of these recent developments, largely because I happen to be familiar with them, though I have no reason to apologize for their importance to anesthesiologists.

1. The Oxygen Saturation and Tension of Normal Arterial Blood and Its Relation to the Alveolar Air

Until recently it was practically universally believed that the arterial blood of normal men at sea level is between 93 and 96 per cent saturated with oxygen, and on the usually employed dissociation curves the corresponding range of oxygen tensions would be from 65 to 80 mm. of mercury. A large number of determinations of alveolar oxygen tension by the procedure in general use (analysis of a single sample exhaled rapidly after a quiet inspiration) has given an average of nearly 110 mm. of mercury for alveolar oxygen tension at sea level. According to these standards there is therefore a tension gradient (ΔpO_2) between alveolar air and arterial blood amounting to some 30 mm. of mercury or more, and considerable speculation has arisen as to its significance.

Recent work has shown that this ΔpO_2 is not a physiologic entity but an experimental artifact due both to undervaluation of the normal arterial tension and to overvaluation of the corresponding alveolar figure. Direct spectrophotometric studies on the arterial blood of dogs and men (5) have shown that the saturation is more than 98 per cent and is usually of the order of 99. Direct estimations of the oxygen tension of such samples have given an average value of 97.1 with a range of 93 to 100 mm. of mercury (6). In the same subjects the alveolar air collected in the manner usually employed (at the end of inspiration) gave an average oxygen tension of 103 with a range of 99 to 112 mm. of mercury. Samples collected at the end of expiration, however, agreed much more closely with the arterial blood, the average pO_2 being 97.4, the range 86 to 104 mm. of mercury (6). One other point of interest was uncovered: a sample of arterial blood that was 99 per cent saturated had a pO_2 (as directly determined) of 98.5 mm. of mercury, although on a standard dissociation curve at pH 7.4 its tension should have been about 120 mm. of mercury. This strongly suggests that there is something wrong with the standard dissociation curves and that they should be redetermined by the improved methods now available.

The reasons for the past errors are presented elsewhere (5, 6, 7, 8) and will not be repeated. The present purpose is fulfilled by pointing out: (*a*) that the figure for normal arterial oxygen saturation at sea level is of the order of 99 per cent instead of 93 to 96; (*b*) that the

normal arterial oxygen tension is of the order of 95 to 100 mm. of mercury; (*c*) that within the errors of the methods used this is equal to the alveolar oxygen tension in samples collected at the end of a quiet expiration; and (*d*) that the end-inspiratory alveolar samples that are very widely used do not give a true picture of the air in equilibrium with the blood leaving the lungs.

2. THE CAUSE OF DYSPNEA

The two occasions in which the respiratory act becomes of immediate importance to the clinician are respiratory insufficiency and dyspnea. The former calls for a discussion of resuscitation, which is too large and complicated a topic to be considered on this occasion. The latter furnishes an excellent illustration of the altered viewpoint mentioned above, for whereas formerly cases of clinical dyspnea were generally attributed to chemical factors acting directly on the respiratory center, they now, with a single exception, appear to be due mainly to reflexes. The exception is inhalation of a carbon dioxide-containing mixture, which is either the result of a therapeutic intervention, an accident, or a laboratory procedure, and can scarcely be regarded as an important clinical entity.

Table 1 has been constructed to document the thesis that abnormalities of respiration predominantly involve factors other than chemical stimuli acting directly on the respiratory center. The various factors listed in the vertical columns are for the most part explained and discussed elsewhere (2, 3, 9, 10), with the exception of Reflexes from the Pulmonary Circulation and Effects on the Cerebral Circulation. The former is a provocative possibility concerning which existing information is highly unsatisfactory. The latter is also in an unsatisfactory state at the present time (see 14) but, with the availability of a method for measuring cerebral blood flow quantitatively in man (11), this situation may be remedied in the near future. This column is included because of its importance to anesthesiologists. The various physiologic, pathologic and anesthesiologic states listed in the horizontal columns are similar in the main to those presented in an earlier publication (10), from which this table is adapted, with the addition of several conditions of special interest to anesthesiologists, viz. oxygen inhalation and voluntary hyperventilation in normal subjects, and anesthesia by several agents, the respiratory effects of which differ fundamentally. The subjects of the physiologic changes listed in the upper seven horizontal columns are assumed to be otherwise normal in condition and environment, and this is also true of the subjects of anesthesia listed in the five columns at the bottom of the table. The disease states and their implications are taken up elsewhere (9, 10). The number of → symbols is intended to portray the importance of this factor relative to the others operating in the condition listed; they do not imply that the intensity of the end-result is necessarily the same as

TABLE 1

		Effectiveness of Stimulant Nerve Impulses from								Body Temperature	Direct Chem. Stim. of Center by		Change in Cerebral Blood Flow
		Lungs			Carotid and Aortic		Cerebral Cortex	Joints and Other Tissues					
		Hering-Breuer	Air Passages	Pulmonary Circulation	Chemo-receptors	Presso-receptors					pCO_2	pH	
Physiologic	CO_2 inhalation			↑?	±						↑↑↑↑	↑?	↑↑
	Acid ingestion				↑↑						↑↑	↑↑?	↑?
	Anoxemia			↑?	↑↑↑↑		↑?			↑?	↓↓	↓↓?	↑↑?
	Asphyxia			↑↑?	↑↑↑↑		↑?			↑?	↑↑↑↑	↑↑?	↑↑↑↑
	Exercise			↑↑?	±		↑↑	↑↑↑↑		↑↑	±	±	↑↑
	O_2 inhalation		↑?		↓↓						?	?	↓↓?
	Voluntary hyperventilation				↓↓↓↓		↑↑↑↑				↓↓↓↓	↓↓	↓↓
Heart disease		↑↑↑↑	↑?	↑↑↑↑?	↑↑		↑?				↑?	↑?	?
Pneumonia		↑↑	↑↑?	?	↑↑↑↑		?			↑↑	±	±	↑↑?
Atelectasis		↑↑↑↑	↑?	?	↑↑						±	±	↑↑?
Emphysema		↑↑		?	↑↑						↑	±	↑?
Pulmon. embolism		↑↑↑↑	↑?	↑↑?	↑↑↑↑						±	±	↑↑?
Asthma		↑↑	↑↑?	↑?	↑						±	±	↑?
Acidosis					↑↑						↑↑	↑↑?	↑?
Anemia									↑?		↑?	↑?	↑
Shock, hemorrhage, etc.						↑↑↑↑	↑?		↑↑		↑?	↑?	↓↓↓↓
Anesthesia by	Ether	↑↑	↑↑↑↑							±	↓↓	↓↓?	↑↑?
	Cyclopropane									±	↓↓	↓↓?	?
	N_2O (anoxic)			↑?	↑↑↑↑					±	↓↓	↓↓?	↑↑?
	Barbiturates				↑↑					±	↓↓↓	↓↓↓?	↓?
	Morphine				↑↑					±	↓↓↓↓	↓↓↓↓?	↓↓?
	Chloralose				↑↑↑↑					±	↓↓↓	↓↓↓?	?

that of other conditions designated with the same number of symbols. The ± sign indicates that this factor may or may not be operative; if it is, it contributes to the end-result but the latter would not be appreciably changed by its presence or absence. The ? mark signifies doubt as to the operation of this factor or the direction of change, either because recent work has weakened confidence in previously accepted ideas (e.g. the stimulation of the respiratory center by hydrogen ions [2, 9, 12, 13] and the supreme importance of carbon dioxide in the intrinsic control of the cerebral circulation [8, 14, 15]) or because of lack of information as to the importance or existence of this factor in the condition listed (e.g. reflexes from the air passages in conditions other than inhalation of irritant agents, reflexes from the pulmonary circulation when it is engorged, impulses from the higher parts of the neuraxis as a factor in rapid, shallow breathing, fever as an element in the effects of anoxemia [see below], and the behavior of the cerebral circulation in pathologic states in man).

The important conclusions to be derived from this presentation are: (*a*) that there is no single, simple, all-inclusive explanation for dyspnea, since the cause varies widely in different conditions; (*b*) that with the exception of intentional or accidental increase in the carbon dioxide tension of the blood (as in carbon dioxide inhalation, asphyxia, and possibly acidosis), increase in the chemical stimulus acting on the respiratory center is not a prominent factor in cases of physiologic or pathologic dyspnea; (*c*) that the most common single cause in clinical dyspnea is excitatory reflexes from the lungs or from the chemoreceptors of the carotid and aortic bodies; (*d*) that in most cases more than one factor is concerned; (*e*) that in some (notably anemia) the tendency to dyspnea has no satisfactory explanation;* (*f*) that anesthetic drugs without exception make the respiratory center less reactive to chemical stimuli, a tendency which may be counteracted by the onset of excitatory nerve impulses (from the lungs and limbs in the case of ether [2, 3], from the carotid and aortic bodies if anoxemia is present), but which otherwise may lead to early cessation of respiration (as with cyclopropane as usually given in a closed system with a high oxygen tension).

3. Stimulation of the Respiratory Center by Anoxia

The evidence that the hyperpnea associated with anoxemia is due to reflexes from the carotid and aortic bodies is overwhelming; that

* In our earlier publication (10) we suggested that the dyspnea of anemia may be due in part to accumulation of acid products of incomplete metabolism in the respiratory center or elsewhere, in part to deficiency of carbonic anhydrase. Both suggestions have been adopted by Wiggers (16), who adds the possibility of reflexes from the chemoreceptors because of insufficient volume of oxygen in the anemic blood. In view of the lack of dyspnea associated with severe poisoning by carbon monoxide (17) or aniline (18) there is no reason to abandon the earlier idea (9) that these receptors are stimulated only when the tension of oxygen in the arterial blood falls significantly, which would not be the case in anemia until respiration became insufficient.

indicating that anoxia is essentially depressant to the respiratory center (apart from reflexes) only slightly less so (8, 9, 19). However, as happens with distressing frequency in the field of respiratory physiology, the steady accumulation of evidence has indicated that the true situation is not nearly as simple as it had been thought to be at first. When dogs with denervated carotids and aorta are made to breathe mixtures low in oxygen, after an initial period of depression their respiratory rates begin to increase and eventually their minute volumes will be back nearly to normal (19, 20) or may go above it (21). When they are brought back to room air their breathing is apt to be greatly increased for some time (21).

It should be made clear that this type of stimulation differs markedly from that seen in the animal with active chemoreceptor reflexes. In the normal animal severe anoxemia causes an immediate and marked increase in depth of respiration and on removal of anoxemia breathing is promptly depressed, perhaps to the point of apnea, with gradual return to normal. In the denervated animal there is a latent period of some four to five minutes during which breathing is depressed, then there is a progressive increase in rate (usually with a decrease in depth), and on removal of the anoxemia, respiratory stimulation comes on gradually and lasts for some time.

These findings are interpreted (21) as indicating that in its direct effects on the cells of the respiratory center anoxia is both depressant and stimulant; that the depressant effect may be overcome by chemoreceptor reflexes or, if they are lacking, by a slow building up of the stimulant process; that when the anoxia is remedied the depressant phenomena are removed more promptly than the stimulant.

There are some other observations that are not in accord with this simple conception. Chiodi et al. (17) found that the severe anoxia produced in men or dogs by the inhalation of carbon monoxide did not cause any hyperpnea, and Clark and his coworkers (18) made practically identical observations on dogs in which severe methemoglobinemia had been produced by the administration of aniline. Both found, however, that the circulation was stimulated and both pointed out that while the respiratory response to severe anoxia apparently depended entirely on reflexes (and therefore did not occur here since arterial pO_2 was normal), the circulatory effects involved something else. That the centers controlling the circulation can be strongly stimulated by anoxia although respiration is only depressed is already familiar from the effects of increased intracranial tension, for when this is raised to a level higher than the arterial pressure, respiration stops almost immediately and without any increase in depth (though a brief period of increased rate may be seen), but the blood pressure then rises until it again reaches a level higher than the intracranial pressure (9, p. 656; 14). It would seem then that some cells in the brain are capable of being strongly stimulated by acute anoxia. Yet while the response of

the vasomotor center to acute cerebral anoxia is of the usual type, that of the respiratory center (deprived of chemoreceptor reflexes) takes the form of an increase in rate whereas the usual protective reaction against anoxemia is an increase in depth. If these stimulant effects are due to intracellular accumulation of acid or other normal chemical excitant, one would expect the respiratory response to be of the normal protective type. The complexity of the situation is further increased by a recent report (22) of the occurrence of marked hyperthermia (above 105 F.) in a flyer who had been exposed to severe anoxemia and in whom no cause other than cerebral anoxia was found for the fever. Perhaps this delayed acceleration of breathing in denervated dogs exposed to severe anoxemia is similar in mechanism and significance to the rapid, shallow breathing that has long been known (23, 24) to occur in patients similarly exposed. Perhaps fever is a prominent factor in both. Clinical observations bearing on the relation between rapid, shallow breathing and fever are desirable.

4. The Effect of Drugs on the Metabolic Activity of the Brain

Several recent studies along these lines have made possible a better understanding of some phenomena that are of paramount importance to the anesthetist. Davis, McCulloch and Roseman (25) applied an oxygen electrode to the exposed cerebral cortex of the anesthetized cat and found that the oxygen tension fell to very low levels during convulsions produced by the electric current or by various drugs. This was interpreted to mean that the increased activity of the cortical cells had brought about a marked increase in the rate at which they utilized oxygen. In our laboratory we (15) have measured the volume of blood flowing through the brain of the lightly anesthetized monkey and have collected samples of arterial and of cerebral venous blood so as to permit measurement of the total oxygen consumption by the brain. The results indicate that cerebral oxygen consumption runs strikingly and consistently parallel with the state of cerebral functional activity, as evidenced by the ocular reflexes, the presence or absence of muscular movements, and the condition of the respiratory and vasomotor centers. We were able to secure (for the first time) trustworthy figures for the oxygen consumption by the brain *in vivo* under different conditions of functional activity. These are summarized in table 2.

From this it is evident that the physiologic range of cerebral metabolism (i.e. that compatible with reasonably prompt and complete return to normal) is from about half to nearly double the resting normal. Recovery from the low level was much more rapid if the depression had been brought about by a narcotic drug (pentothal) than if it was the result of anoxia (hemorrhage). The highest levels were brought about by convulsant drugs (metrazol or picrotoxin), which also markedly increased cerebral blood flow. Of greatest interest was the

regular occurrence, after the convulsions had worn away, of a prolonged period of depression of cerebral functional activity, oxygen uptake, and metabolism. This depression in the oxygen uptake was of about the same order as that produced by a deeply narcotic dose of pentothal, i.e. to about half the resting level, but it lasted considerably longer than did the narcotic depression. As far as we could make out, there were no differences between the depressed state following convulsions and the depressed state caused by cerebral anemia (hemorrhage). We therefore conclude that it is possible to produce anoxia in the brain, with all its consequences, quite as well by increasing the call of the brain for oxygen beyond the capacities of the existing cerebral blood flow to meet it, as by decreasing the supply of oxygen below the existing requirements. This confirms the views expressed by McCulloch and his collaborators (25).

TABLE 2

	Brain		QO_2	Other Organs O_2 Consumption (cc./100 g./min.)		
	O_2 Consumption	Bl. Flow				
	(cc./100 g./min.)					
					Rest	Stimulated
Normal mean	3.7	47	11.1	Muscle	0.3	8.0
Normal minimum	2.5	33	7.5	Heart	0.4	0.7
Normal maximum	4.5	74	13.5	Kidney	0.9	11.0
Highest (picrotoxin convulsion)	6.5	91	19.5	Sal. gland	3.0	10.0
				Pancreas	3.0	10.0
Lowest with recovery (hemorrhage)	1.85	13.2	5.6	(Brain	3.7	6.5)
Moribund	0.39	5	1.17			

These findings have certain therapeutic implications. The dangers of cerebral anoxia are now generally appreciated as far as diminution in the arterial oxygen content is concerned, but little or no attention has been given to the possibility that an effective stimulant may be followed by a more prolonged and perhaps more severe depression than that which it was intended to overcome. In our monkey experiments complete recovery from the effects of pentothal, according to clinical signs as well as cerebral oxygen consumption, occurred distinctly more rapidly when no analeptic was given than it did after a convulsant dose of metrazol or picrotoxin. Continued observation after the awakening effect of the analeptic is therefore desirable, to see if a corresponding situation can be demonstrated in man. Another practical possibility is that in conditions in which cerebral anoxia is unavoidable its effects may be in some measure ameliorated by the judicious use of narcotic drugs, so as to lessen the demand of the brain for oxygen. The circumstances would have to be such that cerebral functions need not be

retained and the underlying condition is not one of spontaneously increasing severity. These requirements are met by severe poisoning by carbon monoxide or by other agents that interfere with the transport of oxygen by the blood (those that form methemoglobin or sulfhemoglobin or other nonfunctioning pigments), by severe hemorrhage or shock or other temporary diminution in cerebral blood flow, and by anesthesia involving anoxemia. The use of sedatives in connection with the latter two conditions is already common, but as far as I am aware they have not been employed in the former. Obviously, their use here would have to be cautious and the chosen agent should have brief, controllable actions. In any case analeptic (convulsant) drugs would appear to be contraindicated under any of these conditions.

One totally unanticipated result of these experiments was the development by Kety (11) of a method for measuring cerebral blood flow by determining the rate at which the nitrous oxide content of cerebral venous blood approaches the arterial during the inhalation of a low concentration (about 15 per cent) of the gas. This procedure has been calibrated against direct measurements of cerebral blood flow in monkeys and has been refined to the point of agreement with the latter within 10 per cent. It has now been used on a number of human subjects, with the following results (table 3):

TABLE 3

Subject	Cerebral		
	A-VO_2 %	Blood Flow	O_2 Uptake
		cc./100 g./min.	
G. H. (multiple sclerosis)	6.2	52	3.2
A. S. (essential hypertension)	4.0	74	3.0
J. P. (gastric neurosis)	10.2	49	5.0
W. G. (normal—at rest)	6.6	66	4.4
J. F. (essential hypertension)	4.7	74	3.5
V. L. (hypochromic anemia)	5.4	56	3.0
L. F. (normal)	6.2	60	3.7

As far as I know, these are the first actual figures for cerebral blood flow and metabolism that have ever been obtained in man. Obviously, the possibilities for obtaining information of immediate importance to anesthetists are very great, and in due course we hope to exploit some of them. At present our energies are being concentrated on other applications of the method.

SUMMARY AND CONCLUSIONS

To show the changes that are transpiring in some of the fundamental bases of clinical anesthesiology several representative examples are cited. They are as follows:

The oxygen saturation of arterial blood of normal men, quietly breathing ambient air at sea level, is of the order of 99 per cent (instead of 95) and its tension is of the order of 97 mm. of mercury (instead of 80 or less). The arterial oxygen tension agrees closely with that of alveolar air collected at the end of a quiet expiration but is lower than that in the end-inspiratory samples that are widely used in this country.

Dyspnea, as produced intentionally in normal subjects in the laboratory or as encountered in the course of disease, is due much more to new or augmented reflex influences than to increased stimulation of the respiratory center by chemical products of metabolism. Anesthetics decrease the reactivity of the center to chemical stimuli but this tendency may be counteracted by reflex factors; if it is not, respiratory failure is likely to be a conspicuous phenomenon of the anesthetic process.

Although the increase in depth of breathing associated with anoxemia is unquestionably referable to reflexes from the carotid and aortic bodies, prolonged exposure to severe anoxemia is able to produce a different type of respiratory stimulation (involving the rate instead of the depth) that apparently is referable to a direct action on the center. The possible significance of this phenomenon is discussed.

Direct studies of the oxygen consumption of the brain in situ have shown that cerebral metabolic activity runs parallel to cerebral functional activity, and that convulsants may lead to cerebral anoxia (with all its consequences) because they increase the oxygen demand beyond the available supply. Possible therapeutic implications of this relation are discussed.

Recent findings bearing on direct measurements of cerebral blood flow and metabolism in man are briefly presented.

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MEETING OF THE AMERICAN SOCIETY OF ANESTHETISTS, INC.

ROOM 440, NEW YORK ACADEMY OF MEDICINE

Fifth Avenue and 103rd Street, New York City

THURSDAY, APRIL 12, 1945

Business Session: 8:15 P.M.

Scientific Session: 8:30 P.M.

Symposium: "Anesthetic Complications and Their Management"—75 minutes.

Major Lloyd H. Mousel, M.C., A.U.S.

Donald Stubbs, M.D., Alexandria, Va.

Joseph Kreiselman, M.D., Washington, D. C.