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Editorial Views

Anesthesia and Metabolism:

A Study of Scientific Interaction

BEFORE DELVING into the finer points of anesthesia and metabolism, as outlined in the papers of this symposium, it is appropriate to reflect on this subject in a general way and to review some of the events that have occurred in its development, hopefully to gain insight as to why there now is such great interest in it. Because this subject has developed in parallel with, and indeed on the foundations of, other disciplines, it is of interest to review the general historical aspects of biologic research before discussing the specific subject of anesthesia and metabolism.

The growth of biologic research can be related to a number of factors working in concert. One is man's insatiable intellectual curiosity which in part has been stimulated by the numerous fascinating and perplexing mysteries of the living scene. This perhaps is one or the basic factors that started and sustained man in his research efforts. Another factor is the fundamental human drive for self-understanding. This has been expanded to include an understanding of the universe in which we live. As research answered the questions growing out of these drives, the store of knowledge increased to the point where man could begin to apply it. The first application of biologic research was to improve agricultural productivity and thereby improve animal and human nutrition. Subsequently, other applications made it possible to alleviate human disease and to increase the span of enjoyable and productive human life.

Other factors responsible for the growth of biologic research include the development of a large number of highly sophisticated research tools. It is fair to say that research advances as the necessary tools are developed. In a similar vein, research grows on itself. Major advances usually are the result of an extremely large number of small bits of information.

The subject of anesthesia and metabolism breaks down into two major topics: 1) the effect of the anesthetic on the normal metabolic pathways, including the enzymes involved in those pathways, and 2) the effect of the enzyme systems on the anesthetic molecule. Although at present it is not entirely possible to discuss one without discussing the other, it has not always been that way. Therefore, first let us discuss the developments in the area of the effects of the anesthetic on the normal metabolic pathways.

Formerly, anesthetics were considered to be substances which exerted their effect solely within the central nervous system. The early theories of narcosis were really thoughts on the effects of the anesthetics on cerebral metabolism. These early theories included the effects of the anesthetics on the permeability of the cell membrane, on cellular proteins, and on oxygen uptake. They tended to be vague because knowledge about metabolism was limited, and knowledge about metabolism had to remain limited until biochemistry as a whole had developed. Truly penetrating questions concerning the biochemical basis of life in turn could not be formulated until the laws of physics and chemistry governing the universe had been elucidated. For this reason, biochemistry is one of the younger disciplines, having its start around the beginning of the twentieth century, after chemistry and physics had become sufficiently advanced to be used as a basis for biochemistry. In the next 50 years, however, the pace of biochemical research quickened. The effort and the resultant information and understanding have been increasing exponentially, and so has our understanding of metabolism.

One of the keys to metabolism has been our knowledge of enzymes. Enzymatic activity has been recognized since early in the nineteenth century. At the beginning of the twentieth century the specificity of enzymes was recognized, followed by the elucidation of the elementary rules of enzymatic catalysis and Sum-

ner's isolation of a crystalline enzyme, urease, in 1926. By the late 1940's and early 1950's, biochemical research was well into the work of isolating and characterizing many of the enzymes in mammals.

At the present time, perhaps the greatest efforts in biochemistry are being directed to problems of the regulation of metabolic pathways. The juxtapositions of component reactions and the control mechanisms necessary to ensure proper supplies of products for biologic functions of the organism are being studied intensively. The general anesthetics have proved useful as tools in these studies because they affect the control mechanisms in some cases. In other cases, they interrupt the pathway in a manner that allows more detailed study of the sequence of that particular pathway. Thus, while biochemistry has aided the study of the anesthetics, it is evident that anesthetics aid in the study of biochemical events. As examples of this, we can cite the effect of the barbiturates and halothane on the mitochondrial electron-transport system, as well as other effects as described in this symposium.

Another aspect of the study of the effects of anesthetics on metabolism relates to the production of pathologic states in the presence of the anesthetic agents—for example, the production of hyperpyrexia. In this instance and others, the study of the effects of anesthetics on intermediary metabolism may uncover abnormal biochemical states.

Let us turn our attention to the other aspect of this symposium, the effect of metabolism on anesthetics. The earliest work on drug metabolism, on the oxidation of alcohols to carboxylic acids, was reported in 1899. However, the principal findings have been made since 1950, and most have been in the last decade. The developments in the area of drug metabolism are closely tied to the study of electron-transport systems. The biochemical work on electron transfer in microsomes had its start with the demonstration in 1949 that microsomes mediated the transfer of electrons from NADH to cytochrome c. The work by Strittmatter on microsomal cytochrome b_5, which started in 1952, was another important step, as was that by Klingenburg and Garfinkel in 1958 concerning the microsomal CO-binding pigment subsequently called cytochrome P_{450}.

The first connection between the microsomal electron-transport system and the oxidation of drugs and other xenobiotics was made by Axelrod in 1954, when he reported the demethylation of sympathomimetic amines and the oxidative deamination of amphetamine to phenylacetone and ammonia. Another important step was the demonstration that the activity of microsomal oxidative enzymes could be increased or "induced" by the administration, *in vivo*, of the substrate in question or of other, often quite dissimilar, compounds. This was the result of work by Brown, Miller, and Miller. Subsequently, Conney and coworkers reported that induction is due to an increase in the enzymes involved. These studies were carried out between 1958 and 1960. The work of the 1960's has expanded on these findings and has resulted in a highly developed, although far from complete, understanding of the events that occur in microsomal drug oxidations.

As early as 1940, the barbiturates were known to be metabolized, but it was not until the microsomal electron-transport system was elucidated that the enzyme system responsible for this was known. On the other hand, since the early work by Haggard, in 1923, the volatile anesthetics had been considered to be inert. Only after the development of some of the early concepts of drug metabolism was it possible to rethink the situation of the volatile anesthetics, and thus it was that in 1962 work was begun in my laboratory to study the metabolism of these agents.

There also are specific reasons for the growth of interest in the subject of anesthesia and metabolism. With the growth of knowledge in the medical sciences has come an increase in the number of available drugs. This, of course, increases the possibility of multiple drug administration and the resulting drug interactions. This has stimulated much research because of a need to know the effects of a single drug before the effects of a combination of several drugs can be assessed. The increase in use of drugs has increased the number of toxicities reported as being caused by drugs. This has also stimulated research on the effects of drugs on metabolism, which raises another point of great importance—much of the stimulus for research comes from

the clinical anesthesiologist through his desire to deliver excellent medical care. It is only by completely understanding the drug he uses that this type of care can be delivered.

Needless to say, not all the answers have been found, and much remains to be done. However, as the papers in this symposium indicate, an excellent start has been made toward understanding the mysteries of the relationship of anesthetics and metabolism.

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Circulation

REGIONAL MYOCARDIAL PERFUSION The application of new therapeutic techniques to the extensive population of patients with coronary atherosclerosis has been retarded by the absence of methods for quantitative assessment of regional myocardial blood flow in man. Coronary cineradiography is widely used diagnostically to localize constrictions or occlusions of large or medium-sized coronary vessels. Unfortunately, radiographic visualization of the diseased artery does not provide information about capillary blood flow in regions distal to the lesion. Thus, neither the adequacy of collateral blood flow beyond the occlusion nor the presence of small-vessel disease can be assessed accurately by arteriography alone. The present report is a description of a method for quantifying capillary perfusion in various regions of the human heart at the time of coronary arteriography. This approach is an extension of a technique previously developed in the dog and consists of injection of ^{133}xenon selectively into a coronary artery and external measurement of isotope washout from numerous discrete regions of the myocardium with a multiple-crystal scintillation camera. The method measures the rate constants of ^{133}Xe washout from many areas of the heart instead of resolving a single multiexponential washout curve, as has been done in the past. Data from 17 patients with normal coronary arteries were obtained by the new technique. ^{133}Xe was injected into right, left, or both coronary arteries. Counts from 294 scintillation crystals viewing the precordium through a multichannel collimator were recorded simultaneously on magnetic tape. Data were processed by a digital computer. Regional myocardial blood flow was calculated for each recording crystal (assuming a blood-to-myocardium partition coefficient of 0.72) and the perfusion pattern was superimposed over a tracing of the subject's coronary arteriogram. Scinti-photographs showing the arrival and washout of isotope from various regions of myocardium and the area of tissue perfused by each coronary artery were obtained by replaying the data tape on an oscilloscope. Significant regional variations in local myocardial perfusion rates were observed in hearts with otherwise-normal coronary arteries. When capillary flow measurements from crystals overlying the various cardiac chambers were averaged for each subject, the mean left ventricular myocardial blood flow (MBF) rate in 17 patients was 64.1 ± 13.9 (SD) ml/100 g/min, which exceeded significantly that of the right ventricle (47.8 ± 10.9 ml/100 g/min) and that of the right atrial region (33.6 ± 10.3 ml/100 g/min). The authors suggest that this approach may facilitate objective assessment of myocardial capillary perfusion in patients with angina pectoris, the effectiveness of antianginal drugs, and the success of surgical procedures designed to revascularize ischemic myocardium. (*Cannon, P. J., Dell, R. B., and Dwyer, E. M., Jr.: Measurement of Regional Myocardial Perfusion in Man with ^{133}Xenon and a Scintillation Camera, J. Clin. Invest. 51: 964, 1972.*) EDITOR'S COMMENT: Once the methods for detailed analysis of organ blood flow have been worked out and techniques for quantifying regional metabolism become available, the concept of a flow ($\dot{Q}$)-to-metabolism (M) ratio will add new dimension to our understanding of function. This will be analogous to the information provided by the $\dot{V}/\dot{Q}$ ratio for the lung.