an adequate description of the location and mode of action of anesthetics. In the mean
time, it would seem tactically wise to advance step by step into the central nervous system
collecting data to locate and describe all the effects, both excitatory and depressant, of
therapeutic doses of the various compounds in the class of general anesthetics.

The paper by de Jong and Nace in this issue of the JOURNAL shows that if anesthetic
doses of ether, methoxyflurane, halothane or nitrous oxide are given to cats already anes-
thesitized with pentobarbital, there is little significant change in the threshold of peripheral
pressure receptors or in the conduction properties of peripheral axons. These results set
the stage for asking more penetrating questions about the mechanisms of sensation and
anesthesia. An immediate question raised by this paper relates to the possible existence of
efferent nerve fibers to skin which might control the sensitivity of cutaneous nerve endings.
Efferent control of peripheral sensitivity has been shown to exist by way of the olivo-
cochlear bundle to the organ of Corti and by gamma efferents to muscle spindles. There is
good evidence that efferents run to the retina in amphibian and birds, and some believe that
they are also present in mammals. No clear physiological or anatomical evidence exists that
efferent systems run to mammalian skin and control sensitivity, although frog skin sensi-
tivity does seem to be affected. However, clinical evidence in causalgia and Raynaud’s
disease does suggest very strongly that the autonomic nervous system is involved in patho-
logical peripheral sensitivity either by delivering efferent nerve impulses to the periphery
or by providing a pathway for especially important afferent impulses. The work of de
Jong and Nace provides the control base from which to test the possible effect of autonomic
afferents on normal peripheral sensitivity. In

their preparation, the presence of barbiturate
would decrease the various autonomic reactions to be expected from the anesthetics
administered. Furthermore, the gallamine used
to block neuromuscular transmission would
also block transmission at sympathetic ganglia
and therefore abolish whatever peripheral ef-
fects might have occurred from alterations of
autonomic outflow. Now that it has been
shown that the anesthetics used have no direct
effect, it will be extremely interesting to see in
the decerebrate unanesthetized and unpara-
lyzed cat if they have an indirect effect by way
of the sympathetic outflow. Once these
experiments have been completed, it will be
possible to begin an analysis of changes in first
central cells.

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On the Measurement of Myocardial Contractility

Within the last few years, the cardiovascular
literature has been infused with a substantial
volume of terminology that, while not new,
was formerly restricted almost wholly to pa-
ers on muscle mechanics. Many of those
who are not directly involved must have
wondered just how much the appearance of
expressions like “sliding filament model,”
“force-velocity curve,” and “active state”
should be influencing their understanding of
myocardial function. While it is true that
the terms are sometimes brought into cardio-
vascular writing as little more than fashionable
window-dressing, it is equally true that the
basic concepts behind them can be very useful
in clarifying one’s thinking about the perform-
ance of the heart.

Consider the problems of defining precisely
what constitutes a change in myocardial con-
tractility, and of choosing the most meaningful
index of contractility for a given experimental
situation:

The term “myocardial contractility” is used
so often that few of us are bothered by the
fact that it is almost never defined. We are all quite sure of what it means, or so we believe until we stop to think about some specific questions. For example, does a change in the performance of the heart resulting from a change in end-diastolic fiber length constitute a change in myocardial contractility? I think most people would answer that it does not, but I doubt that this would be a unanimous judgment. For those who say it does, what about the influence of the change in fiber length that occurs as the ventricle ejects blood during the course of a single beat? Are we to consider myocardial contractility as something that is normally changing during the course of each contraction? The amount by which fiber length changes during a contraction is normally influenced to a great extent by factors outside the heart—by aortic pressure in the case of the left ventricle. Should changes in ventricular performance due to factors totally external to the heart be considered as changes in myocardial contractility? I think few would ascribe to a change in contractility the drastic change in the function of the left ventricle produced by clamping off the aorta. This example is extreme, but it is not as ridiculous as it might seem at first, for in hemodynamic studies ventricular stroke work is one of the most commonly used indices of ventricular function, and is frequently used as the chief, or even the sole measure of myocardial contractility. Yet stroke work is highly subject to modification by changes in the pressure opposing ejection. Since work is the product of a pressure and a volume, the ventricle does no work when it ejects blood with no opposing pressure; similarly, it does no work when the pressure is so high that ejection is prevented altogether. If the pressure opposing ejection is varied from one of these extremes to the other, stroke work rises from zero to a maximum, then falls to zero again. These changes in stroke work are entirely attributable to changes in factors outside the heart. Of course, changes in stroke work may also result from changes in the properties of the myocardium itself, and changes in aortic pressure may directly or indirectly produce such changes. The important point is that changes in stroke work need not reflect changes in the properties of the myocardium.

In a paper in this issue of Anesthesiology, Shimosato, Gamble, and Esten were faced with the problem of interpreting changes in ventricular stroke work occurring in the face of changes in ejection pressure. They came, quite correctly, to the conclusion that under such circumstances changes in the "ventricular function curve" do not necessarily indicate changes in the contractile state of the myocardium. Problems of this sort should certainly make one question the widespread use of ventricular stroke work as an index of myocardial contractility, yet that measure has been so generally adopted that few authors seem to feel it necessary even to explain or justify its use. The feature of stroke work that probably accounts for its appeal is that it combines in a single measure the two most distinctive aspects of muscular contraction—tension development and shortening. The fact that these two variables tend to vary in opposite directions when the load on a muscle is changed lends a further superficial plausibility to the use of stroke work as an index of contractility. The damning fact is that the relation between tension and shortening is not a simple inverse proportionality, and for this reason (as well as others) ventricular stroke work does not remain constant as ejection pressure is varied. (For further discussion see references 1 and 2.) Other simple indices of contractility may lack popularity because they seem less adaptable to a variety of experimental situations, but they have the advantage at least of misleading nobody. How, then, can one characterize a change in myocardial contractility in terms that will be more fundamental and generally applicable? First, it will be necessary to frame a specific definition of what does and what does not constitute a change in myocardial contractility. In doing this, and in choosing an index of contractility most appropriate to the conditions of a particular experiment, it is useful to consider a few basic concepts of muscle physiology. Though these concepts were originally derived from work with skeletal
muscle, there is now ample evidence that they apply also to mammalian cardiac muscle.

The sliding filament mechanism (e.g., 3) of muscular contraction is now solidly established. The basic contractile machine of striated muscle consists of interdigitating arrays of thick (myosin) and thin (actin) filaments which slide past one another as the muscle changes its length. The development of tension is thought to result from the establishment of cross-bridges (at sites that are visible with the electron microscope) between the two types of filaments. The number of potential cross-links varies with the degree of overlap between the thick and thin filaments, and therefore with muscle length; and over a wide range, tension development varies with muscle length in a way that is strikingly consistent with the sliding filament mechanism. Thus the length-tension curve of active muscle (which is the basis of Starling’s law of the heart) is largely understandable in terms of the structure of the contractile machinery, and describes what must be regarded as one of the most fundamental properties of striated muscle.

A second fundamental relationship is that between the tension in an active muscle and the speed with which it shortens, described by the force-velocity curve. Empirically it is observed that the faster a muscle shortens, the less tension its exerts, or conversely, the heavier the load on a muscle, the more slowly it lifts that load. In a simple way, the basis for such a relationship might be visualized in terms of the sliding filament mechanism as follows. The tension in a muscle is a function of the fraction of the pool of potential actin-myosin cross-links that are attached at a given time. When shortening occurs, cross-links must be broken and reformed as the actin and myosin filaments slide past one another. The process of breaking and reforming a cross-link takes a finite time, so the faster the muscle is shortening the smaller will be the fraction of cross-links attached at any given time, and the lower will be the tension exerted. Clearly the details of the force-velocity relation and of its modification by various agents will figure significantly in the eventual development of an understanding of the molecular interactions in the cross-links, but the general nature of the relationship is also important in predicting the gross behavior of muscle in various experimental situations. (It is, after all, the force-velocity relationship that is mainly responsible for the fact that stroke work varies with load in the way that it does.)

The third fundamental concept of muscle physiology that will be useful for this discussion is that of the active state. Actually the term “active state” is a very general one, and it is easy to read more into it than perhaps one should. As such, “active state” means nothing more than the state in which the contractile machine is turned on. The “intensity of the active state” has an explicit and very limited definition (the tension in the muscle when the contractile elements are neither lengthening nor shortening) so I will use the more general term “degree of activation” to refer to the extent to which the machine is turned on without specifying whether or not shortening is permitted to occur. A rough indication of the time course of the active state, and one that is adequate for many purposes, is given by a high-speed tracing of the ordinary “isometric” contraction (which is not really isometric because of the “give” or compliance of elements in the muscle that are mechanically in series with the contractile elements). However, the degree of activation at any moment can be described completely only in terms of a relation between force and velocity. (As the active state waxes and wanes during the course of each contraction, one can imagine a force-velocity curve growing up out of the origin of the graph, and then collapsing back into it.)

The time course of the active state probably reflects the appearance and disappearance of ionized calcium in the cytoplasm bathing the contractile filaments. Calcium is thought to be released into the cytoplasm during the action potential; the ion is apparently involved in the establishment of cross-links between actin and myosin; relaxation occurs when elements of the sarcoplasmic reticulum then sequester the calcium by an active transport process.

Taken together, the three fundamental relationships just discussed (length-active ten-
sion, force-velocity, and time course of the intensity of the active state) provide a fairly complete description of the mechanical behavior of muscle and a reasonable framework for an understanding of it. Four variables (force, velocity, length, and time) are involved, all of which may be changing simultaneously during the course of a single contraction. It has been proposed 2 that a change in myocardial contractility be defined as a change in the performance of the heart that results from a change in the relationships among these four variables during the active state. This definition does not provide any simple way of measuring changes in contractility, but it does provide an objective criterion for deciding whether a given change should or should not be regarded as constituting a change in myocardial contractility. Under the definition, the effects of changes in the fundamental properties of the contractile machine are considered to represent changes in contractility, while changes in performance arising solely from conditions outside the heart are not. For example, changes in ventricular performance resulting from changes in end-diastolic fiber length or in the resistance to ejection are not changes in myocardial contractility, while the effects of temperature changes, sympathetic nerve stimulation, catecholamines, cardiac glycocides, anesthetics, and many other drugs are. However, it is only a first step to decide whether or not a given intervention produces a true change in myocardial contractility. As Rushmer 4 has pointed out, it is a dangerous oversimplification to describe a given change in the performance of the heart only as an increase or a decrease in contractility. To do so is to lose sight of important differences between the effects of different interventions, any of which may reasonably be described as increasing or decreasing contractility. One must go on to provide a complete description of the changes produced; this is inescapable, whether one describes the changes in the terminology of hemodynamics, or of muscle physiology. The relations among the four variables during the active state can be influenced in various ways, and a thorough characterization of a change in myocardial contractility requires a full description of the changes. Probably the most satisfactory way to do this is in terms of the length-tension curve, force-velocity curve, and time course of the intensity of the active state. Obviously, it is not often practical or even possible to determine these curves, particularly in clinical situations. Nevertheless, from relatively simple measurements, such as high-speed tracings of isometric contractions or of ventricular pressures in the intact circulation, it is usually possible to deduce a good deal about the sorts of fundamental changes that must be going on in the myocardium. It would be a great step forward if investigators abandoned the habit of thinking of myocardial contractility as something to be assessed in terms of some particular index, and regarded their measurements only as ways of getting an idea of the changes occurring in the fundamental four-dimensional relationship that is at the heart of the matter. The various measurements that can be made all provide glimpses of that relationship; some provide better glimpses than others, and the window that provides the best view in one situation may not be best for the next. Certainly, a better picture can be pieced together from several different glimpses than from one alone.

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References
Maternal Hyperventilation During Labor

The possibility that maternal hyperventilation might have an adverse effect on fetal oxygenation and acid-base state is of particular interest to the anesthesiologist.

Many women hyperventilate during labor in response to painful contractions or undue apprehension. Shallow panting breathing is an integral part of auto-hypnosis in Lamaze's technique for painless childbirth, and may lead to overventilation with tingling, dizziness or even carpal spasm. During elective cesarean section, active hyperventilation is practiced by some anesthesiologists, more in Great Britain than in the United States, in the belief that it is of benefit to the infant.

The first evidence that maternal hyperventilation might be harmful for the fetus was obtained in 1960 when attempts were being made to improve the oxygenation and acid-base state of human infants delivered at elective cesarean section by lowering maternal PaCO₂. Experiments on pregnant guinea pigs confirmed these findings, but the mechanisms involved were not all delineated. More recently Motoyama and his co-workers have extended the investigation of this phenomenon and their findings published in this issue of the JOURNAL provide new and interesting information. These authors suggest that alteration of pH rather than PaCO₂ might be the controlling factor, influencing placental vascular resistance and intraplacental shunting as well as the maternal and fetal oxygen dissociation curves.

Evidence questioning the harmful effect of maternal hypocapnea on the fetus has recently been published in the Lancet. Following relatively short periods of hyperventilation when the maternal PaCO₂ decreased to a mean level of 15.7 mm. of mercury and the pH increased to 7.62, 18 infants were delivered by elective cesarean section, apparently in excellent condition. The author, however, ignored the greater degree of acidosis and low oxygen levels in infants whose mother's pH was 7.65 or higher. These infants were already clearly adversely affected, although not to a degree to cause clinical depression. Had the hyperventilation continued for longer, their condition would undoubtedly have deteriorated.

It is worthwhile to point out that in the original study of Moya and his co-workers, only 2 infants of 61 were depressed (25 patients were studied before the first depressed infant was observed). Although severe degrees of maternal alkalosis were not seen during spontaneous breathing, this has now been observed. A very apprehensive mother was discovered to have a PaCO₂ of 16 mm. of mercury and a pH of 7.64. This was not ameliorated by epidural anesthesia. The initial capillary sample from the fetal scalp had a pH of 7.32. During the next 2 hours fetal pH fell to 7.13 followed by the passage of meconium. Emergency mid-forceps delivery was performed and the infant had an Apgar score of 1.

While a brief period of maternal alkalosis might not adversely affect the fetus there is no evidence that this is beneficial and at the same time there is considerable evidence of its potential danger. In the light of present knowledge it would seem prudent to avoid willful hyperventilation at all times. Until all the mechanisms involved in this phenomenon have been clearly defined, the skeptical physician should satisfy his curiosity by studying experimental animals.

A number of unanswered questions still remain, particularly the effect of maternal pH or PaCO₂ on uterine vascular resistance and