The concept of safety that accounted for the changed complexion of clinical anesthesia at the middle of the twentieth century accounted also for the specific goals of research in anesthesia. This single aim of increasing safety for the total patient undergoing anesthesia was held alike by clinical anesthetists who constantly strove to refine their technics, by pharmacologists, physiologists and physicists in university research centers whose investigations in pure research were directed to the synthesis of new agents and a better understanding and control of the physiologic effects of those in use, and by anesthesiologists who sought through research to solve specific clinical problems. The discovery of new agents and new technics for their own sake was without purpose considering the availability of those of proved value. The motivation for research was to find in new agents and methods specific desirable qualities lacking in those in use. The same was true of the investigation of drugs and technics of adjunctive value in the care of patients undergoing anesthesia.

When research in anesthesia is viewed in this light, it is not surprising that few investigations of new anesthetic agents had shown promise since the synthesis of divinyl ether and cyclopropane and the introduction of intravenous thiopental sodium anesthesia during the early 1930's.* In inhalation anesthesia only three investigations deserve mention, and none of them had significant application in clinical work. In the pharmacology department of the University of Maryland, John C. Krantz, Jr., and his associates con-

*In 1934 trichlorethylene, a chlorine-substituted derivative of ethylene, was suggested by D. E. Jackson to have use for general anesthesia and analgesia. Although used rather extensively in Great Britain, particularly for obstetric analgesia, it was not marketed in the United States until 1952. (Jackson, D. E.: Study of analgesia and anesthesia with special reference to such substances as trichlorethylene and vinylthene (divinyl ether) together with apparatus for their administration, Anesth. & Analg. 13:198, 1934.)
ducted research on the "newer" ethers for the purpose of synthesizing an ether-hydrocarbon compound of anesthetic properties similar to those of ether but lacking ether's irritating qualities. This work was in progress over the greater part of the fifth and into the sixth decade of the century. In 1951, at the University of Iowa College of Medicine, clinical trials of xenon, a stable and relatively inert gas byproduct of the manufacture of oxygen and nitrogen, showed it to have anesthetic properties. However, the principal value of the discovery was that the gas promised to be useful in studies leading to a better understanding of the anesthetic process. During 1952, at the Mayo Foundation, Albert Faulconer, Jr., revived investigations of the administration of nitrous oxide and oxygen under pressure to achieve through this means the simultaneous administration of full anesthetizing doses of nitrous oxide and an atmosphere rich in oxygen. The sole new anesthetic agent accepted in clinical practice during this almost 20-year period was the intravenous anesthetic Surital Sodium, a thiobarbiturate synthesized by Parke, Davis & Co. and first used clinically in 1950 by M. Helrich and associates. It was claimed for this new barbiturate that recovery from its effects was more prompt than from those of thiopental sodium, and that the tendency toward laryngospasm was reduced. A theoretical goal for investigators of other barbiturates was the synthesis of an agent whose effects, unlike those of thiopental sodium and Surital Sodium, would not be cumulative.

The greatest strides in pharmacologic research in anesthesia during the fifth decade of the century were made in connection with adjuncts to anesthesia. Of these, all were secondary to the investigations of curare and synthetic curare-like compounds as muscle relaxants. The ability to use an agent without narcotizing or hypnotic properties for the production of the needed muscular relaxation for surgical operations made possible the limitation of the administration of general anesthetic agents for the purposes of producing unconsciousness and insensibility. Various compounds of the active principle of crude curare, tubocurarine, were developed by pharmaceutical houses, and by the end of the decade two effec-

tive synthetics, decamethonium bromide (Syncurine) and flaxedil were on the market. The advantages to the synthetics were that the amount of active principle would be more constant and the source of the material more reliable. As was true of projected research on barbiturates for intravenous use, a goal of further pharmacologic studies of muscle relaxants was the minimization of cumulative effects.*

Advantageous as was the use of muscle relaxants in connection with anesthesia, their paralyzing effects, particularly on respiration, were not without danger, and pharmaceutical research was directed to the discovery of antidotes. The earliest of these was physostigmine, which in 1900 was discovered to be a pharmacologic antidote for curare. An antidote for decamethonium bromide was found in pentamethonium bromide, an agent that was, however, not without danger. The most effective antidote was synthesized in 1950. This agent, tensilon chloride, was a highly specific anticurare agent for tubocurarine compounds and flaxedil, although it was not effective against decamethonium bromide.

Other important pharmacologic and clinical researches on adjuncts to anesthesia were in relation to the use of procaine and procaine amide, for the relief of pain and for the prevention and the treatment of cardiac arrhythmias, and the use of ephedrine preparations, for the control of hypotension during anesthesia. From Sweden, anesthetists received dextran, a large molecule polysaccharide, and from Germany, periston to be used as plasma substitutes for the treatment of hypotension from shock.

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*Diacetylcholine (succinyl choline) gave promise of having the desirable property of lack of accumulative effects, in the light of investigation being conducted during 1952.
As certain side issues to physiologic research, other discoveries were made that contributed similarly to increased safety for the surgical patient. In 1949 administration of serum albumin was found to be a specific treatment for postanesthetic encephalopathy from cerebral edema. Research in cardiac physiology led to the development of specific routines for resuscitation when cardiac arrest occurred in the operating room. The results of such investigations deserve mention because they were applicable immediately to the reduction of mortality and morbidity from clinical anesthesia. But the fundamental challenge of physiologic research in anesthesia—the elucidation of the phenomena of anesthesia and the site of action of anesthetic drugs—had by the middle of the twentieth century failed to stir up much enthusiasm, although some investigators had found valuable clues in the effects of anesthetics on acetylcholine within the cell membrane.

The most spectacular research investigations of the period were in relation to the application of physics to anesthesia and the use of equipment made possible by discoveries in electronics. The findings that the pattern of brain potentials in electro-encephalographic studies was related closely to the depths of anesthesia, and that the first signs of impending cardiac and respiratory depression were revealed by changes in electro-encephalographic patterns, had two applications: first, controlled objective studies of the effects of anesthetics upon vital functions, rather than subjective impressions of degree of muscular relaxation and depression of reflex action; and, second, the use of electro-encephalography as a diagnostic measure during anesthesia to forestall the occurrence of adverse neurocirculatory effects. Also, from electro-encephalographic and electrocardiographic studies of the anesthetized patient, in conjunction with the analysis of anesthetic gas mixtures with an acoustic gas analyzer and investigations of blood levels of anesthetic agents and


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oxygen tensions, objective data were accumulated to elucidate the optimal combinations of anesthetic agents and oxygen required for safe effective anesthesia.

The application of physics to clinical anesthesia also brought about the development of a practical oximeter for the continuous recording of arterial oxygen saturation during anesthesia,\textsuperscript{13} respiration for the mechanical control of respiration during thoracic operations,\textsuperscript{14} and the pneumotachograph to enable the anesthetist to observe the frequency, amplitude and character of respiration during anesthesia.\textsuperscript{15} Another application of biophysics to anesthesia was the development of the technics for continuous spinal anesthesia\textsuperscript{16} and for continuous caudal analgesia for obstetrics.\textsuperscript{17}

Research in the sources and control of static electricity and in the combustibility of anesthetic gaseous mixtures and of ether peroxides led engineers closer to the elimination of explosion hazards in hospital operating rooms. Deaths from mix-ups of gas cylinders on anesthesia machines drew on the combined efforts of commercial enterprise, national organizations of anesthetists and the American Hospital Association to devise yoke pins for gas cylinders that would prevent such accidents.

In an analysis of the direction that research in anesthesia was taking at mid-century, several factors are paramount, all again being related to the central concept of safety. The procedures of anesthesia are not therapeutic and only in a few instances, such as in the control of pain, are they diagnostic or palliative; primarily, anesthesia is the servant of therapeutic and diagnostic surgery and, as a servant, is subject to the requirements of the master. Consequently, the aims of research in anesthesia are of necessity confined, first, to the development of anesthetic agents and technics that would provide the optimum in safety for the patient, optimal operating conditions

\textsuperscript{17}Hingson, R. A., and Edwards, W. B.: Continuous caudal analgesia: An analysis of first ten thousand confinements thus managed with report of authors' first thousand cases, J.A.M.A. 129:538, 1943.
for the surgeon and minimal deleterious effects on the patient's vital functions; second, to refinements in preoperative preparation and postoperative care, again to protect the patient insofar as possible from the unavoidable insults of surgery and anesthesia; and, third, to the repair of damage when the effects of the operation and the anesthesia are injurious.

In the work toward these goals the most significant trend was in the direction of substituting objective for subjective data on the effects of anesthetic agents on the human organism by the application of physical methods of mensuration. The immediate results were not spectacular, but the indications were that a wealth of pertinent facts applicable to clinical anesthesia could be collected through this means.

A second significant factor in the research goals was the drive to eliminate human error by the substitution of electronic devices for the senses of the anesthetist in the detection of cyanosis (oximeter), cardiac depression (electrocardiograph) and cerebral depression (electroencephalograph). The costliness of the necessary apparatus made its routine application impracticable in many departments of anesthesia, but information drawn from its use acted as a constant reminder to anesthetists of the fallibility of their senses. Serving the same end was clinical research on cardiac resuscitation, correction of shock and hypotension and correction of postanesthetic encephalopathy from anoxia.

The search for anesthetic agents and muscle relaxants with specific desirable qualities over and above those of agents in current use had its principal attraction for pharmaceutical houses and suppliers of anesthetic gases, and clinical research on new agents was stimulated largely by such commercial enterprise. If it were necessary to give a reason for this fact, it would be that investigators had a long way to go to fill in the gaps in the understanding of the effects and proper use of accepted agents.

Finally, it may be said that the complete realization of the overall aim of research in anesthesia—maximal safety for the patient and optimal operating conditions for the surgeon—would be a sterile hope if the education of the clinical anesthetist did not keep pace. The qualifications of the practicing anesthetist remain the principal determinants of whether the patient will be safe and the surgeon satisfied.