The general theme of previous Crawford W. Long Lectures has been "creativity and discovery in medicine." My subject for this fourteenth lecture, anesthetic mortality, is clearly the antithesis of creativity. Study of mortality, however, is the traditional and fundamental method of studying disease, leading to discovery of new diseases, their causes, prevention, and effectiveness of therapy. In the sense, then, that examination of mortality leads to discovery, I have taken a critical look at studies of anesthetic mortality.

I discovered, first, that a profound bias has pervaded and continues to pervade all studies of anesthetic mortality. Although we glibly quote an incidence of anesthetic mortality, and even believe we can subdivide it into primary and contributory, we do not in fact know how most of these people died. We cannot even define anesthetic death. Second, this same bias has remarkably exempted anesthetic drugs from several fundamental clinical pharmacologic concepts applicable to all drugs, particularly the concept of risk/benefit.

It is of more than historical interest that the first systematic study of anesthetic deaths was conducted by John Snow, that remarkable nineteenth-century physician. In 1858, his posthumously published book, On Chloroform and Other Anaesthetics, contained probably the best study of anesthetic mortality ever recorded. Snow not only collected all known cases of presumed anesthetic death, but he reported all of them in detail. When in doubt as to cause, he conducted his own experiments to verify that the reported events could lead to death. When insufficient information was available, he simply gave no judgement. As will be seen, few studies since then have included this degree of documentation. Few investigators since then have had the ability not to make a judgement. No study since then has included experimental verification of a proposed cause of death.

Mortality studies since Snow's are largely irrelevant to questions posed by modern anesthetic practice; therefore, my thesis relates solely to the anesthetic era that began during World War II. The typical inquiries into anesthetic mortality up to that time was the study of Trent and Gaster, published in 1944, which I cite randomly as an example of the then state of the art. They reviewed 54,000 anesthetics administered in their hospital between 1930 and 1943 and tabulated sudden deaths in the operating room. Of the 38 instances collected, 11 were attributed to surgical causes such as shock, hemorrhage and infection. Of the remaining 27, one death followed aspiration of vomitus, and 26 deaths were listed as cause unknown. These 26 were then considered anesthetic deaths and were analyzed by age of the patient, anesthetic agent, technique, and operation to arrive at some estimate of the relative safety of the various anesthetics.

A significant change in this pattern occurred in 1945, when Henry Ruth urged the establishment of anesthetists study commissions, of which there were only two at the time (Philadelphia County Medical Society and Ohio Society of Anesthetists). The primary purpose of such a commission was educational, according to Ruth, who wrote:

Therefore a constant interchange of thought is indicated between surgeon, internist and anesthesiologist in the best interest of patients. Intramurally, this is accomplished by staff conferences. The formation of anesthesiologists study groups achieves the same object between institutions by a discussion of fatalities occurring from anesthesia and other interesting anesthetic situations.

In practice, the commission, a body of anesthesiologists, surgeons, and other physicians, reviewed all cases that were submitted voluntarily. He describes their method of review:

At the conclusion of the discussion, a vote is taken to determine, first, whether the majority believe that fatality is preventable or unpreventable, both from the point of view of anesthesia. Only preventability from anesthesia is recorded [italics added]. For example, a purely surgical death, acknowledged by the surgical consultants and visiting surgeons, would be classified as unpreventable from the point of view of anesthesia. If the fatality is voted preventable, a further vote is requested to decide the factors which may have initiated or led to death. These may include overdose or improper selection of anesthetic agent or method, errors in technic in the application of the anesthetic agent, lack of or improper supportive measures during anesthesia or improper postanesthetic care.
Here, then, was the beginning of a bias that by definition all anesthetic deaths were preventable. The commission had little trouble making these decisions. Of cases submitted, 67 per cent were preventable, 22 per cent unpreventable, and only 11 per cent were deferred for additional information.

Despite the stated educational objectives, Ruth's summary concluded:

The probable foremost benefit is the direction of the attention of the medical profession to fatalities occurring from improper anesthesia and its mismanagement [italics added] which otherwise would be considered attributable to other causes. If the inclusion of study groups of this character were functioning more generally, a more accurate estimate of the mortality rate from anesthetic practices could be obtained.

Here, now, began the search for errors. Unless it was preventable, unless there was an error, there was no anesthetic death.

This theme was repeated more vociferously when Robert Macintosh published his devastating article, "Deaths under Anesthetics," in 1948. Macintosh had been the recipient of the first Chair of Anesthesia in the world and anesthesia practice in Britain was considered at that time the most highly developed in the world. He wrote:

In my experience one of the unprofitable sidelines of a department of anesthetics is the testing of new drugs, for the first time, on the human subject. . . . As I hold that there should be no deaths due to anesthetics, I am very uneasy as to how far we are justified in testing new drugs when the correct administration of those already available to us will give excellent operating conditions to the surgeon at negligible risk to the patient. I believe that patients would be better off if research of new anesthetic drugs was halted for five years. . . .

My opinion that anesthetic deaths are preventable was originally based on my experience and on personal incidents related to me by colleagues. It was confirmed during the war when I travelled round visiting RAF hospitals in different parts of the country. I took the opportunity of calling at a number of provincial hospitals and heard of local tragedies. I found that what might be described as stock accidents were happening all over the place, and very understandable and successful efforts were made to hush them up.

He supported his views by presenting a collection of anesthetic horror stories. Toward the end, he attacked the British coroner system which requires all deaths during anesthesia to be reported to the coroner:

One of the main functions of the coroner is to protect the public against murder or manslaughter. The possibility of murder with anesthetics on the operating table is so small as to be disregarded. I have never heard of a verdict of manslaughter, and yet I am satisfied that it would have to be brought in frequently if the coroner was more searching in his questions and if the anesthetist in the witness-box embarrassed him by telling the truth, the whole truth and nothing but the truth; for let us face up to it, the anesthetist doesn’t go out of his way to tell the whole truth.

He concludes with—

Every region should have a Committee to study anesthetic deaths with the object of preventing similar tragedies elsewhere, but let it be small and chosen with care. A pathologist and anesthetist should certainly be on it. But in research of this nature let us beware of putting too much faith in laboratory scientists; it might be better to add a psychologist or a sympathetic G.P. to whom the anesthetist is more likely to open his soul.

Here, then, is the world’s leading anesthetist, saying very explicitly in 1948 that 1) all anesthetic deaths are preventable, 2) errors are the cause of all anesthetic deaths, 3) laboratory scientists have little to contribute to discovery of the cause of death during anesthesia, and 4) anesthetists involved in such events do not tell the truth. This was the prevailing bias when I began my training in anesthesia. This bias has pervaded all studies of anesthetic mortality since then, and we labor under it to this day. Let us examine some of the studies that followed.

The first systematic study of the death rate from anesthesia after World War II was the remarkable Beecher–Todd study. Designed with great foresight, this was a landmark in the methodology of clinical investigation because it was multilocal, with ten participating institutions: prospective, reflecting current anesthesia practice, rather than retrospective; multidisciplinary; and included large numbers (almost 600,000 anesthesias). All deaths were reviewed for surgical and anesthetic error. When no error was found, the death was classified as the result of patient’s disease. Anesthetic deaths were not defined, but examples were provided as to the types of situations to be included. The examples consisted mostly of errors, but also included the categories inherent toxicity and abnormal drug sensitivity, which I mention only because they illustrate a foresight not present in other studies. Unfortunately, they gave no description of any of the 384 of their so-called anesthetic deaths, nor even a tabulation by cause, except for their "curare deaths." Their "anticurare" bias was so strong it overshadowed other biases and made all their data generally suspect. No prospective study of anesthetic deaths has been undertaken since.

As the Macintosh article led to studies of anesthetic mortality in Britain, the Beecher–Todd report provoked many subsequent studies in this country. They have been of two general types: 1) The retrospective review within one or more institutions. In these studies the total number of anesthesias was known and an incidence of anesthetic mortality could be derived. 2) The case-submission studies. In these the total number of anesthesias from which the cases were drawn was unknown, and an incidence could not be
calculated. The general method used in all these studies were the error-seeking techniques of the Study Commissions and the Beecher-Todd Report, overlayed with Macintosh philosophy. A postsurgical death was reviewed by a committee or, at times, by an individual. The review consisted of a search for errors in surgical or anesthetic management; finding neither, death was ascribed to the inexorable course of the patient’s disease. “Errors” were considered any departure from whatever was considered optimal anesthetic management at the time of review. A cause-effect relationship between “error” and death was not necessary to label a death anesthesia-related. Let me cite some of the biases actually recorded in these reports. The Baltimore Anesthesia Study Committee asked the following questions of each submitted death report: Did the anesthetic management contribute to the death of this patient? If yes, which phase of the anesthetic management was principally at fault? Five choices were given for classifying the fault or error and all anesthetic deaths were included in some error category. Without an error, anesthesia did not contribute to death. Details of these judgements were unrecorded, and no allowance was made for a subsequent review based on changing concepts of care or new knowledge. There were always more errors than deaths.

Another aspect of the prevailing preventability-error bias is described in the report of Dripps, Lamont and Eckenhoff. They wrote in 1961:

There is nothing to be gained in a mortality study by omitting a particular death merely to lower a statistical death rate. Avoiding responsibility or taking refuge in the fact that a patient was desperately ill prior to anesthesia and operation may improve one’s mortality figures, but it will not advance general knowledge or change one’s own practice.

Here we have the view that improvement in anesthetic practice would follow if anesthesiologists would substitute for denial a generous acceptance of responsibility for the unfavorable outcomes of operations.

The 1970 publication of the Special Committee Investigating Deaths under Anaesthesia® (in New South Wales) spelled out its bias very clearly.

In those cases, classified in categories 1, 2, and 3, the Committee has held that the anesthetic was in part or wholly responsible for the patient’s death. This implies that there has been some error in judgement, management or technique on the part of the anesthetist and these cases have been analyzed according to the errors thought to have been involved.

They then identified 1,215 errors in the 286 deaths. These were classified in 12 broad categories such as inadequate preoperative preparation, inadequate resuscitation, incorrect choice of anesthetic, inadequate ventilation, etc. Unique to this study is the fact that the committee’s opinion as to errors in each death report was made available to the responsible anesthetist. In 49 per cent of the anesthetic deaths, the responsible anesthetist disagreed, probably with vehemence, with the committee’s judgement of error. Of final interest is one major conclusion of this report, which states:

Anesthetic agents themselves are not lethal except when they are misused.

In only two studies were the judges not completely omniscient in determining the causes of death. In 26 of 745 deaths in all categories of the New South Wales study, the cause could not be assessed despite considerable data. In the Dripps, Eckenhoff and Lamont study, ten of their 80 anesthetic deaths were classified as

No anesthetic or surgical error in light of present knowledge.

They never explained, however, why these ten were considered anesthetic deaths. Nobody else seemed to have trouble finding errors and placing the blame somewhere.

Obviously, then, studies designed to discover only errors discovered an extraordinary number of errors, most of which are unknown today. This would not have been so bad if only they had described, even briefly, the circumstances of the deaths leading to these judgments, as Snow did. Only four studies include any description whatsoever of the events involved. Considering the vast changes in surgical and anesthetic practice, concepts of surgical care, and the rapid acquisition of new knowledge about anesthetics, even in the past ten years, these data are frankly uninterpretable today. How would they have judged the administration of morphine, 2 mg/kg, to a sick cardiac patient? What would they have thought of treating heart failure with a hypotensive agent? We have no idea what they thought about anything. They never recorded it.

Obviously human errors play a role in anesthetic mortality. But it is important, in today’s onerous malpractice climate, to know whether anesthetic deaths attributable to error amount to 10 or 90 per cent. The high estimates of error in all these studies resulted from failure to entertain the possibility of any cause of death other than error, and particularly, the loose equating of any “departure from current practice” with error and anesthetic death. From the brief details of some judgements included in a few published reports, the relationship of an identified error to a death strains one’s cause-effect imagination.

Despite this general criticism, the reporting of errors clearly pointed to some patterns of anesthetic death which are in fact errors, without any doubt as to cause
and effect. For example, deaths from obstructed endotracheal tubes, intubation of the esophagus, failure of oxygen supply, disconnected ventilator, and air embolism. Here, there is little equivocation as the mechanisms of death, and they are clearly preventable. Fortunately, knowledge of these errors had led to development of methods to prevent such errors; for example, non-kinking endotracheal tubes, improved cuffs, fail-safe oxygen delivery systems, and plastic infusion systems. On the other hand, when errors were identified, as they usually were, in terms of "inadequate preparation of anesthesia" or "hypotension," little of educational value and nothing of value in identifying mechanisms or methods of prevention was derived.

Lest one believe the error bias is no longer with us, allow me to quote from a now widely cited Closer Lecture by W. D. Wylie, which appeared in the Annals of the Royal College of Surgeons of England in 1975. He reviewed cardiac arrests reported to their Medical Defense Union, a study similar to the United States study of Gordon, Larson, and Prestwich, published a year ago. Wylie wrote:

The headings (a classification of primary causes of cardiac arrest) are based on my opinion of the primary causes of cardiac arrest but they reflect Sir Robert Macintosh's oft-quoted view that the causes of anaesthetic deaths are all too often mundane and obvious and rarely require much, if any, scientific investigation to establish them, provided a truthful account of the facts can be obtained.

As late as 1975, Dr. Wylie reiterated and endorsed Macintosh's conclusions. Neither he nor his predecessors ever seriously entertained the possibility that anesthetic deaths might result from something other than mundane errors. He continues the myth that anesthetic drugs are different from all other drugs, absolutely safe unless someone errr. This simply is not in accord with what has been going on in clinical pharmacology these past 30 years.

This innocuousness of anesthetics and the error bias assume, first, that drugs used during anesthesia are not characterized by idiosyncrasy, adverse reactions, or interactions with other drugs or with disease states. The bias states that adverse responses appear only when the drugs are misused. No doubt this concept derived vicariously from the once-widely-held concept that inhalational agents were completely inert, not metabolized, and could be put into or withdrawn from the circulation at will. Since they were inert, how could they be harmful? The naïveté of this assumption is equivalent to that of believing that antibiotic toxicity is always an overdose error unrelated to the severity of infection, or that digitalis toxicity is always an error unrelated to the severity of heart failure. Unfortunately, the same naïveté characterizes some current drug surveillance studies, which ascribe all untoward events in patients treated by medication to adverse drug reactions, whether or not a cause–effect relationship can be demonstrated and independent of the stage of disease treated. These attitudes completely ignore well-established principles of clinical pharmacology, such as the variations in responses to average doses, influences of specific diseases on drug responses, drug interactions, enzyme induction, active drug metabolites, and pharmacogenetics, all of which until recently were not even conceived of as applying to anesthetic drugs in man. The recurrent theme for anesthetics has been "they are not lethal unless misused." Drugs used in clinical anesthesia are potent and potentially lethal and like all other drugs, have primary desired actions and unwanted side actions. At times side actions become unintentionally severe and noxious; that is, they become adverse drug reactions, and at times adverse drug reactions are fatal. Fatalities from drugs, anesthetic or otherwise, even when cause and effect can be demonstrated, are not tantamount to error. For example, atropine, 0.2 mg, was given to treat sudden bradycardia and hypotension secondary to traction reflex in a digitalized patient with mitral stenosis during vaginal hysterectomy with spinal anesthesia. Instead of the anticipated result of this logical action, severe tachycardia and pulmonary edema developed, resulting in death. Clearly, this was an adverse drug reaction. It was not an error, but was related to the hazard of administration of atropine to patients who have mitral stenosis. Suppose a commission concluded that a vasopressor should have been given: it was, and excessive hypertension with pulmonary edema and death ensued. Was giving either drug an error? Drugs, like all other therapeutic modalities, are prescribed in anticipation of benefits and at the risk of adverse reactions. There never has been any justification for exempting anesthetic drugs from this basic therapeutic principle, which applies equally to anesthetic techniques. For example, profound muscle relaxation was necessary to permit a surgeon to relieve severe intestinal obstruction in a seriously ill patient. This relaxation was achieved by large but conventional doses of muscle relaxants. Failure to breathe after operation was an accepted risk, and its consequence was prolonged intubation and mechanical ventilation. When such a patient experiences bilateral bronchopneumonia and dies several days later, the prior use of large doses of muscle relaxants does not constitute an error, or even an adverse drug reaction; it was simply a risk necessarily taken to effect a treatment it was hoped would be life-saving. The same argument applies to aspiration of vomitus, which, we all agree, cannot be prevented 100 percent of the time, and therefore cannot always be an error.

A second implication of the error bias is that it explicitly precludes any new knowledge concerning mech-
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Anesthetists of deaths attributable to anesthesia. I indicated the few reports in which deaths not obviously due to any error were even mentioned. Reviewers of death protocols never entertained the possibility of undescribed and subtle mechanisms by which anesthetics could contribute to mortality. It is worth noting that discoveries of major new mechanisms of anesthetic deaths during the past 15 years have not followed from any study directed to anesthetic mortality by review of death reports. Succinylcholine-induced hyperkalemia, malignant hyperpyrexia, genetic variants in plasma cholinesterase, post-halothane hepatitis and methohexitone-induced nephrotoxicity were discovered by alert clinicians inquiring into adverse effects not attributable to error. One can properly wonder how deaths from these causes were classified by omniscient committees before these mechanisms were described. One can also wonder how many more mechanisms not the result of error remain to be discovered. Possibly the role of anesthesia in surgical mortality is greater than anyone has yet imagined. The most obvious roadblock to the discovery of these mechanisms is the fact that with rare exceptions, anesthesia is not therapeutic, and is administered only to facilitate another mode of therapy. No control study of the hazards of operation without anesthesia or conversely, anesthesia without operation, will ever be performed. The hazards of anesthesia can therefore never be considered independent of a second procedure. Both risks and benefits of anesthesia are confounded with a disease, an operation by a second set of persons, and finally, a third set of persons who care for patients while they are still vulnerable to adverse effects of anesthesia. In this complex interaction of procedures and personnel, it is difficult to identify adverse effects of anesthesia alone, particularly in patients with serious systemic disease undergoing hazardous operations.

Discovery of other mechanisms in anesthesia mortality may be more feasible in a less complex milieu, for example, a study of anesthesia limited to patients not expected to die. Every experienced anesthesiologist can probably remember a patient who underwent a non-life-threatening operation and died unexpectedly during or shortly after operation. For example, suppose a 50-year-old man undergoing subtotal gastrectomy could not be resuscitated after cardiac arrest during operation. According to the death record, prepared by the anesthesiologist, preoperative, anesthetic and surgical management was impeccable. Necropsy revealed diffuse mild coronary disease without occlusion, chronic bronchitis, and duodenal ulcer. None of these can account for death. How can such an event be explained? These are only three possibilities. First, death was fortuitous and part of the obligatory mortality of hospitalized patients, which I discuss below. The second possibility is that death was caused by a mechanism yet to be discovered. The final alternative, if we maintain our present bias, is that the anesthesiologist who prepared the death report lied, and no "scientific investigation" is necessary. To me this last possibility is no longer intellectually tenable. The image of the guilt-laden anesthesiologist accepting all unanticipated outcomes of operation as a consequence of his error has become counterproductive. Progress requires that reports be accepted as true accounts, that they be collected in a repository or registry, that cause-effect relationships be sought according to rigorous scientific standards, and that ignorance be admitted when no cause can be found.

Parenthetically, let me add that I believe we have created our own malpractice problem by perpetuating this bias and failing to apply the type of analysis I have just outlined. Too often, I have been a second reviewer on a malpractice claim in which a first consultant had no trouble deciding the cause of cardiac arrest was "hypoventilation." This despite the complete absence of a single shred of evidence from the records or depositions that such was the case. Obviously, the first consultant knew the only cause of cardiac arrest was error, and concluded that the anesthetist simply lied in his deposition.

I mentioned earlier an obligatory death associated with hospitalization.16 This has never been considered in any study of anesthetic mortality. It has been estimated that 350,000 Americans die annually with "sudden death syndrome." This is defined as unexpected natural death occurring within an hour after collapse of an individual in apparent good health. Assume that 16 million operations are performed annually with a mean hospitalization of five days, and assume the day of and day after operation are the vulnerable periods for anesthetic mortality. Then there are 32 million man-days during which any of the 350,000 "sudden death syndrome" events could be considered anesthetic mortality. Almost all sudden deaths have been assumed to be the result of fatal arrhythmias secondary to coronary-artery disease. Yet recent studies reveal a disconcerting number that cannot be accounted for by necropsy findings of coronary-artery disease. For example, sudden death without necropsy evidence occurs from the recently discovered syndromes of mitral-valve prolapse, coronary-artery spasm or Prinzmetal's angina, and prolonged QT interval. Sudden deaths not the result of heat stroke occur every fall among football players without necropsy evidence to account for death. Unexplained sudden death among healthy soldiers is well known. Crib deaths (sudden infant death syndrome) presents a similar enigma in infants who show no cause of death at necropsy. Certainly, sudden death syndrome cannot account for a large number of deaths associated
with anesthesia. But its great significance is the fact that it exists at all and that it is a potential cause of death during anesthesia. It means that anesthetic death should never be a diagnosis by exclusion. It means that anesthetic causes must be reasonably related to a death before a judgement of anesthetic death is accepted.

What do we know about the role of anesthesia in surgical mortality? Precious little. Thirty years of self-flagellation in the form of anesthetic mortality studies have generated an abundance of "errors." Most of these now exist only in the vague memory of committees who equated deviation from accepted practice in 1960 or 1970 with "error" and equated "error" with anesthetic death. The need for evidence of a causal relationship was waived in the belief that inclusion of even the most remote relationships would improve standards of practice. Perhaps it did; it also created our malpractice problem. Knowing the bias that generated these data, all published estimates of the incidence of error or the incidence of anesthetic deaths are now unacceptable. In my opinion, these incidences remain unknown.

A fresh approach is needed. The practice of anesthesiology consists of the administration of a variety of potent drugs, employment of a number of technical maneuvers requiring skill, and utilization of mechanical equipment requiring knowledge of its function and malfunction. In every aspect of this activity, something is actively done to a patient. At any phase of this activity, any untoward event may be attributed to an immediately preceding action by simple post-hoc reasoning. In less activist medical specialties untoward events are readily ascribed to the patient's disease or an unrelated fortuitous event. However, the almost continuous ministrations of the anesthesiologist leave him highly vulnerable to the easy post-hoc hypothesis. Demonstration of a cause-effect relationship is absolutely essential if any secure knowledge of mechanisms of anesthetic deaths is to be achieved. I believe it is time to substitute for the presumption of guilt a presumption of innocence until cause and effect are demonstrated.

Further, the anesthesiologist's application of drugs, manipulations and machines to patients must be viewed on the same risk/benefit scale as all forms of therapy. Each is designed to benefit total surgical care of a patient. But each also has its risk in terms of adverse drug reactions, unwanted outcomes of technical maneuvers, and malfunction of machines, including the risk of receiving and acting on erroneous information from monitors. Risks exist because they are not completely preventable by the most skilled and knowledgeable human beings. Patients do not respond to drugs with stereotyped responses but with spectra of responses, at times adverse. All human beings are not anatomically the same, and all technical maneuvers cannot be consistently successful. Machines do not perform optimally at all times. There are mishaps that may occur at the hands of the most competent anesthesiologist, using drugs and techniques faultlessly and conscientiously. These mishaps alone or in combination may lead to anesthetic death, without error and without toxicity. The risks of precisely these mishaps need to be quantified to delineate the role of anesthesia in surgical mortality.

Finally, more attention needs to be given to the sudden death syndrome in any hospital population. Activist specialties such as anesthesiology and surgery are absorbing these deaths as related to their treatments. Not only do these deaths confound estimates of risk and mortality, but they lead to malpractice litigation and costly defensive anesthetic practice, which does not represent optimal anesthetic care.

Most important, we must finally rid ourselves of the error bias that we have borne for 30 years, and look at anesthetic administration in the same light as we need to look at influenza vaccine, saccharin, and adding TRIS to mattress and clothing to make them nonflammable. To every benefit, there is a risk. The only way to guarantee immunity from risk is to do nothing at all.

References