THE ANAESTHESIA LABORATORY OF THE HARVARD MEDICAL SCHOOL
AT THE MASSACHUSETTS GENERAL HOSPITAL

BY
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This laboratory is 21 years old this year and should by now have "come of age", but it is with some hesitation that I describe (on request) its activities, not because I am fearful that others may pick up leads and pursue them successfully—indeed that would fulfill a major purpose of the laboratory—but because of a natural reticence to describe one's activities in detail to the reader lest he seem to have an exaggerated idea of their significance. Whether or not our excursions into the laboratory have been successful is beside the immediate point. I am impelled to discuss these things because it seems that a sufficient number of investigators, especially young investigators in the field of anaesthesia, do not appreciate what a rich harvest awaits their work.

According to the late Mr. Vincent of the Rockefeller Foundation, "Doctors don't reason: they just rearrange their prejudices." There is no deterrent as good as a laboratory in preventing the easy arrangement of prejudices as a substitute for reasoning. I should like to describe the Anaesthesia Laboratory in terms of what we are doing and where we are heading. While the quality of our teaching may or may not be at once much influenced by the presence of research activities, I am sure it will be in the end. It is quite clear that we have had a better selection of residents to choose from because of these activities. Such considerations are therefore pertinent to an "Educational Number" of this Journal.

A NEGLECTED AREA IN MEDICINE

It is fitting that research in anaesthesia at the Massachusetts General Hospital should be an integral part of the institution, for, as though to celebrate the Hospital's silver jubilee in 1846, Morton's research with a fish, a dog, and one, Gilbert Abbott, produced the hospital's first great scientific contribution—a demonstration that is recognized over the world as a milestone in the progress of civilization. Notwithstanding its auspicious introduction into clinical medicine, anaesthesia as a field for scholarly study remains a neglected area.

Some insight into the importance of this neglect can be obtained, perhaps, by taking a look at the results of the study that Beecher and Todd (1954) conducted in ten university hospitals. A careful on-the-spot examination of more than a half million anaesthetic administrations over a five-year period indicated that the death rate associated with anaesthesia (anaesthesia deaths were so designated in each of the ten participating hospitals) is about 1:1650. Curiously, while numerous dissenting opinions were expressed as to the causes of the deaths, no serious challenge was raised of this order of magnitude of deaths in which anaesthesia played a prominent part, taking into account the high proportion of the cachectic, ill and aged in the usual university hospital in this country. While the patient's problems in the university hospital are more serious than the average, so also probably their care is better. One can extrapolate this roughly to cover all of the 7,000,000 anaesthetic administrations carried out in the 160,000,000 population of the United States each year. We then find that twice as many citizens die of anaesthesia as died in this country each year from poliomyelitis in the prevaccine era. When one considers the millions rightly spent each year on poliomyelitis research (and the success achieved) compared with the small sum spent on anaesthesia, the need for giving attention to research in anaesthesia is evident.
GOALS OF THE ANAESTHESIA LABORATORY

Anaesthesia in its death-dealing power is a neurological "disease". Its sought-after primary effect is, of course, depression of the central nervous system; to an extraordinary extent anaesthetic secondary or toxic effects strike through the nervous system. For example, even a complication apparently unrelated to the nervous system, like the accumulation of fixed acids in the blood as a consequence of ether anaesthesia, can be prevented, as Brewster et al. (1952) have recently shown in dogs by block of the nerve pathways to the adrenal glands. Even when these pathways are blocked, one can clinch the proof by injecting the secretion of the adrenal glands, adrenaline, in physiological amounts and show how this then results in the accumulation of fixed acids in the blood. The key to the understanding of most of the good and the bad powers of anaesthetic agents lies in the nervous system.

There are three goals of the Anaesthesia Laboratory: one is to study the problem of irritability (responsiveness) of the tissues to stimuli and the suppression of this irritability by drugs—as fundamental a problem as exists in all biology; and second—a practical problem—to lower the death rate from anaesthesia. Third, we believe that the thoughtful approach to problems necessary in a laboratory improves our teaching and the conduct of our department.

Let us consider the practical problem for the moment. How can the practical goal best be achieved? One point of view might be to go at once to a study of the complications of anaesthesia: for instance, how often and why does spinal anaesthesia cause severe headache, and why are some paralyses permanent after spinal anaesthesia, as in the cauda equina syndrome? Such studies are needed and they are important; but to attack them is to attack the symptoms of the "disease", not the "disease" itself. In any case, funds are readily available from a number of sources for relatively short-term studies of this kind.

In the long run, far greater distance will be covered and more of lasting value accomplished if a long-range attack can be made upon the basic problem stated in the first goal: study of the primary effects of anaesthesia, study of what the anaesthetic process does, and what anaesthetic agents do to the nervous system in terms of basic pharmacology and physiology.

THE BROAD FIELD

Those not previously familiar with our work might wonder at the variety of the attacks being made on the problem at hand. The rationale of this several-phase attack becomes clear when it is realized that what can be studied profitably are the central nervous system depressants as a group. It is customary to divide these up into sedatives, hypnotics (the sleep producers), analgesics (the pain relievers), antitusives (cough suppressors, surely related to the analgesics), ego depressants (agents used in "truth serum", so-called), and anaesthetics (Beecher, 1957). The needlessness of a rigid preservation of these several categories becomes apparent when it is realized that, for example, nothing more than an increase in dosage of a barbiturate is adequate to take a patient through this gamut from sedative to anaesthetic. A useful cross fertilization of ideas comes from related work in these several categories.

SPECIFIC NEUROPHYSIOLOGICAL STUDIES

I shall describe how we have attacked the problems presented by anaesthetic and related agents, and how we hope to continue, handicapped as we are in planning and in holding research teams together by short-term grants.

(1) Techniques which make possible a study of the white matter of the central nervous system. In animals, Rudin and Eisenman (1951) showed in this laboratory that various spinal cord tracts could be easily dissected over lengths of 10–15 cm and removed to a nerve chamber where the character of the action potentials and metabolic peculiarities of central nervous system white tissue could be studied for as long as 24 hours. They have shown that these tissue masses are adequately oxygenated by diffusion alone and that spike potential properties are normal. In order to establish the fact of adequate oxygenation, studies were carried out which involved elevated tensions of oxygen. While the point was demonstrated...
with tensions slightly exceeding one atmosphere, deleterious effects of the oxygen were encountered at two atmospheres and studied extensively at eight. This led to a series of observations (Rudin and Eisenman, 1952) which demonstrated that “oxygen poisoning” produces changes consistent with increased permeability of the cell membrane with loss of intracellular potassium and accumulation of it in the intercellular area. These techniques can now be applied to a study of the effects of anaesthetic agents on the cell membrane. This is very important. All evidence to date indicates that normal conduction of nerve impulses requires a normal membrane. The fundamental problem is how anaesthetic agents alter membrane properties and thus conduction of nerve impulses. Rudin and Eisenman (1951) have also characterized the normal after-potential sequence of this tissue and have found it strikingly different from that of peripheral nerve, notwithstanding many assumptions by others to the contrary. Associated with this difference there are some very interesting special responses of this tissue to altered ionic environment. This revolutionary new technique makes available a new class of neural tissues (white matter) for electrical and pharmacological study of the effects of anaesthetic agents on the central nervous system.

(2) Study of the electrical activity of the central nervous system in sleep and in wakefulness and as influenced by anaesthetic agents. Brazier’s (1951) work in this laboratory on the effects of barbiturates on the electrical activity of the brain; in particular, her demonstration that with the onset of sleep the origin of the electrical activity shifts from the occipital to the frontal region (Brazier, 1949); her new method of measuring depth of sleep, and the effect of hypnotic agents upon this, as well as the work (Brazier and Beecher, 1952) on motility during sleep and the effects of drugs on this, are all fundamental attacks upon the basic problems of the primary effects of the central nervous system depressants.

(3) Work on the mechanism of pain relief. Other work in this laboratory on animals (Beecher et al., 1939) laid the basis for our current explanatory hypothesis as to how barbiturates in small doses can block pain in man (Keats and Beecher, 1950), presumably by block of internuncial neurones, producing a temporary, reversible, pharmacological lobotomy. (The similarities of this state with surgical lobotomy are striking). This hypothesis (loc. cit.) needs further study as a basic approach to an understanding of the mechanism whereby pain can be relieved. We have made the assumption that full perception of the experience of pain requires intact association paths, long circuiting, reverberating nerve impulses, intact internuncial neurones, to put it into neurophysiological terms.

(4) The neurological control of respiration. In work interrupted by World War II, Beecher and Moyer (1941) studied the mechanisms of respiratory failure under barbiturate anaesthesia and, in particular, the variability of the Hering-Brewer reflexes under barbiturates (Moyer and Beecher, 1942a). Central stimulation of respiration by anoxia was also demonstrated, apparently for the first time (Moyer and Beecher, 1942b). Study then was directed at the cellular level to the effects of oxygen tension on the metabolism of cerebral cortex, medulla and spinal cord (Craig and Beecher, 1943a), and to the effect of low oxygen tension on tissue metabolism (Beecher et al., 1942; Craig and Beecher, 1943b). High oxygen tensions were studied at toxic levels in Drosophila (Williams and Beecher, 1944). These basic studies led easily to practical studies of the respiration described below in the section on metabolic problems. Practical procedures of anaesthesia for thoracic surgery were summarized by Beecher (1951).

(5) Circulatory changes. Early circulatory studies began with changes in brain volume produced by anoxia and hypercapnia during anaesthesia (White et al., 1942) and progressed to a study of lymph formation and flow (Beecher et al., 1942; Beecher and McCarrell, 1943; Polderman et al., 1943). General circulatory studies involved problems arising from increased pressure in the airway (Beecher et al., 1943). The influence of anaesthesia on the circulation (Bennett et al., 1944) laid the foundation for a long series of wartime studies on “The Physiologic Effects of Wounds”, published as a separate volume in the Surgeon-General’s history of World War II.
CURRENT WORK

Three fairly distinct areas have gradually emerged from the early work in this laboratory: the metabolic studies are now the principal interest of Dr. John P. Bunker and his associates. The circulatory and hormonal studies are Dr. William R. Brewster jr. and his group's field of interest. The writer, with his colleagues, has for a decade limited most of his investigation to quantitative work on the mental and psychomotor effects of the central nervous system depressants. We have thus prolonged and concentrated interests of a given individual in a given field and yet broad coverage of three widely different areas of importance to the development of anaesthesia.

While we have been fortunate in having the full-time association of physiologists and chemists—their names are recorded in the attached bibliography—it is a firm rule of this laboratory that all members of it who are anaesthetists, however great their interest in basic science may be, regularly administer clinical anaesthesia and participate in teaching, both didactic and clinical. We believe that in this way the laboratory's interests and activities enrich our total programme.

METABOLIC EFFECTS OF ANAESTHESIA

For some years this work has been under the direction of Dr. John P. Bunker. Our interest in the metabolic effects of anaesthesia, extending over a considerable period, has led us into a variety of studies. As early as 1940 we were interested in problems of gas exchange during thoracic surgery (Beecher and Murphy, 1940) and were the first to call attention with data to the serious heights to which the carbon dioxide tension could rise when the pleura was open. The fears of Waters, of Crafoord, of ourselves and others of the inadequacy of carbon dioxide elimination using the then current anaesthetic techniques were well founded. Moderate to severe respiratory acidosis was observed during ether anaesthesia with the open chest. Simultaneously, moderate to severe degrees of metabolic acidosis occurred, and this observation further stimulated our interest in the metabolic effects of anaesthesia.

Our initial objective was to determine whether anaesthesia was responsible for the metabolic acidosis or whether the metabolic acidosis was in some way related to the respiratory acidosis. Van Slyke and others, many years previously, had demonstrated severe metabolic and respiratory acidosis in dogs during ether anaesthesia. We have confirmed the occurrence of a metabolic acidosis in the etherized dog, but at the same time have found that in using modern anaesthetic techniques a respiratory acidosis did not occur (Bunker et al., 1951). The next step, a translation of these studies to man, brought out interesting differences. We found with uncomplicated, closed chest anaesthesia that neither a respiratory nor a metabolic acidosis occurs in the normal adult under ether (Beecher et al., 1950). This is true also for cyclopropane as far as a metabolic acidosis is concerned, but under this agent a respiratory acidosis does occur unless the respiration is assisted (Stormont et al., 1942). A metabolic acidosis does not occur under thiopentone anaesthesia (Bunker et al., 1951; Bunker, 1956). On the other hand, infants and small children respond to ether with a metabolic acidosis characterized by high serum lactate and serum pyruvate concentrations (Bunker et al., 1952); and adults themselves under abnormal circumstances (cirrhosis, Cushing syndrome) may develop moderate to severe metabolic acidosis during ether anaesthesia (Bunker et al., 1953).

An attempt has been made to understand the mechanism of these disturbances (Brewster, 1952; Henneman and Bunker, 1957a, b). It was found (Brewster et al., 1952) that a total sympathetic nerve block in the epidural space with dilute procaine, was able to prevent completely the metabolic acidosis, the high serum lactate, serum pyruvate, and in addition, the hyperglycaemia of the etherized dog. The role of reflex action involving the sympathetic nervous system during ether anaesthesia in the dog was thus strongly implicated. Metabolic studies in man, however, suggest that this mechanism may be of little or no importance. Slight but consistent elevations in serum lactate and pyruvate (in addition to the well-known hyperglycaemia) which have been observed during ether and cyclopropane
in the adult might be caused by a reflex outpouring of adrenaline, but changes in serum citrate, alphaketoglutarate, and inorganic phosphorus were found to be in the opposite direction of those produced by adrenaline (Henneman and Bunker, 1957a, b).

Metabolic disturbances may develop during surgery from causes other than the anaesthetic, and these are of considerably greater danger to the patient than any produced by well conducted anaesthesia. Moderate to severe elevations of serum citrate, lactate, and inorganic phosphate during massive blood replacement of surgical haemorrhage have been observed (Bunker et al., 1955). Elevations of citric acid may depress ionized calcium sufficiently to depress cardiac function seriously and possibly sufficiently to prolong clotting (Bunker et al., 1955); however, simultaneous disturbances in all phases of coagulation have been observed and these are of significance in the occasional occurrence of uncontrollable oozing from the surgical field (Bunker et al., 1956, personal communication).

An opportunity to compare the effects of anaesthetic agents on the impaired liver has been of interest. Our original conclusion, based on pre-operative and postoperative liver function tests, "that as far as the liver is concerned, anaesthesia is a very small part of the sum of stresses which add up to the total operative insult" (French et al., 1952) has been confirmed by further clinical studies. Venous shunt surgery for the relief of portal hypertension is followed in this hospital by a 25 per cent incidence of postoperative liver failure. During the ten years, up to 1954, studies were made of 140 shunts or attempted shunts, all performed by a single surgeon. The anaesthetics were very evenly spread among ether, cyclopropane, and hypotensive spinal anaesthesia, both as to numbers of patients and severity of pre-operative liver disease. The incidence of postoperative liver failure, as well as the operative mortality, was almost exactly the same for the three different anaesthetics (Ebeling et al., 1956).

The experience we have had in studying metabolic effects of anaesthesia has provided a useful guide for the study of new and controversial techniques as they have been introduced: for example, induced hypotension, hypothermia, and the extracorporeal circulation technique. In carefully chosen patients, hypotensive spinal anaesthesia has produced remarkably little disturbance in acid-base balance, renal, or liver function (Greene et al., 1954). Disturbances in psychomotor function have given cause for alarm, but in a group of patients undergoing surgery of equal magnitude (pelvic exenteration, splenorenal shunt, etc.) under anaesthesia with normal blood pressure, similar, if less frequent, disturbances were observed (Greene et al., 1954).

During uncomplicated hypothermia, in variance with recent reports in the literature, Henneman and Bunker (1957a, b) did not observe metabolic acidosis. When major vessels are occluded, blood transfusions are given, and shivering is allowed, then metabolic acidosis can and does occur. The use of citrated blood is particularly dangerous during hypothermia. Utilization of citrate is depressed as part of the overall slowing of metabolic processes; in addition, as suggested by preliminary observations by Brewster in this laboratory, the hypothermic heart is less able to tolerate a rise in citric acid or a fall in ionized calcium.

Current metabolic studies in this laboratory, under the direction of Dr. John P. Bunker, include: the effect of anaesthesia on liver blood flow using the P32 technique of Dobson and Jones (1952) (in collaboration with Dr. George Nardi of the Department of Surgery); the mechanism of antidiuresis during anaesthesia; the immediate physiological disposition of sodium citrate and of calcium chloride, infused independently into experimental subjects and operative patients; disturbances in blood coagulation produced by multiple blood transfusions.

NEUROLOGICAL AND HORMONAL EFFECTS ON THE CIRCULATION

Work in this area is under the direction of Dr. William R. Brewster, jr. We have had a longstanding interest in the physiological response of the organism as a whole to both the anaesthetic agent and the hormonal and ionic changes which accompany the stress associated with anaesthesia and surgery.

Work in this laboratory has demonstrated, as
mentioned, the importance of the role played by the sympathetic nervous system in the haemodynamic and metabolic response of the dog to the administration of di-ethyl ether (Brewster et al., 1952; Brewster and Isaacs, 1953). In the normal animal the positive inotropic effect of adrenaline and noradrenaline, released reflexly from the adrenal medullae and cardiac sympathetic nerve endings, was found capable of antagonizing the direct depressant effect of ether upon the contractility of ventricular heart muscle. The reflex sympathetic response is essential for the optimal maintenance of the contractility of ventricular heart muscle and is essential for maintenance of the cardiac output at the ether concentrations required for all planes of "surgical" anaesthesia. In animals in which the reflex sympathetic response was affected by an epidural sympathetic block, the direct myocardial depressant effect of di-ethyl ether was found sufficient to produce critical depression of the contractile force of ventricular heart muscle and cardiac output at arterial ether concentrations of 100-130 mg per cent. It is thus evident that the neuroendocrine response of the animal, involving the reflex release of adrenaline and noradrenaline from the adrenal medullae and the sympathetic nerve endings in heart muscle, together with an optimum positive inotropic effect of adrenaline and noradrenaline, are factors of primary importance. It was inferred that the clinical safety of ether as an anaesthetic agent was in part dependent upon the neuro-endocrine response of the mammalian organism.

It has been repeatedly demonstrated that all general anaesthetic agents exert a negative inotropic effect directly proportional to their anaesthetic potency and concentration. This fact suggests that the activity of the sympathetic nervous system, through reflexly released adrenaline and noradrenaline, is a factor of primary importance in the maintenance of optimal contractility of heart muscle, and blood flow during the administration of general anaesthetic agents.

Not only is the positive inotropic effect of reflexly released adrenaline and noradrenaline essential in order that the organism tolerate high concentrations of di-ethyl ether, but the same fundamental principle is operative in the presence of elevations in arterial carbon dioxide tensions. In the animal in which a total sympathetic block has been produced either by the epidural injection of a 0.4 per cent procaine solution, or by intravenous ganglionic blocking agents (hexamethonium, pentolinium, or trimetaphan), the maximum carbon dioxide tension that can be tolerated varies between 80-90 mm Hg. When the arterial carbon dioxide tension is elevated above 40 mm Hg in these animals, there is a progressive decrease in contractility and resultant blood flow. As in the case of the intact dog during di-ethyl ether administration an elevation of the arterial carbon dioxide in the normal dog is accompanied by an increased reflex release of adrenaline and noradrenaline. The positive inotropic effects of the latter counteract the direct myocardial depressant effect of carbon dioxide, permitting the animal's heart to tolerate a carbon dioxide tension of at least 240 mm Hg.

The above work points towards a major principle. In the mammal, there are several distinct levels of permissible chemical insult. These levels are low under the circumstances of a total sympathetic block. They may be radically elevated in the presence of normal sympathetic activity.

More complete knowledge of the differential sympatho-adrenal response of the dog, the infant and adult man to such stimuli as di-ethyl ether, increased blood carbon dioxide tension, decreased blood pH, and to other chemoreceptor and baroreceptor stimuli is greatly needed. Recent work reported by Dr. Henry Price (1957) at the University of Pennsylvania has demonstrated that a sympathetic response occurs both in the dog and in adult man during ether administration. He reported an interesting fundamental difference, however, in the character and magnitude of the response. The dog was shown to release adrenaline and noradrenaline both from the adrenal medullae and sympathetic nerve endings. Adult man responded primarily with the release of noradrenaline from sympathetic nerve endings with no appreciable adrenal medullary release of either adrenaline or of noradrenaline.

Implications drawn from the response of the sympathetic nervous system, as described above, suggested the need for a complete study of the
endocrine and ionic variables which might affect
the haemodynamic and metabolic response to
adrenaline and noradrenaline. The first endocrine
interrelationship to be studied was that existing
between adrenaline, noradrenaline and the thyroid
hormones (Brewster et al., 1956).

The importance of the role of the sympathetic
nervous system in relation to the physiological
alterations observed during anaesthesia has led to
a study of the haemodynamic and metabolic inter-
relationships in the end-organ activity of adrena-
line, noradrenaline, the thyroid hormones and the
adrenal cortical steroids. It was found that the
physiological alterations of thyrotoxicosis, pre-
viously attributed to the direct effects of the
thyroid hormones per se, are indeed due to the
physiological activity of adrenaline and noradrena-
line. This conclusion was reached by demonstrat-
ing that thyroid feeding produced the classical
haemodynamic and calorigenic effects of hyper-
thyroidism including significant increase in the
heart rate, oxygen consumption, cardiac index,
and effective ventricular stroke work.

The metabolic and haemodynamic effects of
thyrotoxicosis could be abolished by preventing
the reflex release of adrenaline and noradrenaline
with a total sympathetic block. Studies done
during a one to four-hour period of total sympa-
thetic block demonstrated that there was no
significant difference in the oxygen consumption,
cardiac indices, heart rates, average right or left
auricular mean pressures, ventricular stroke work,
and arteriovenous oxygen differences of the
thyroid fed dogs as contrasted with the euthyroid
group of dogs.

All parameters of activity of l-adrenaline and
l-noradrenaline were found to be increased by
increased concentrations of the thyroid hormones.
The infusion of either l-adrenaline or of l-nora-
drenaline into thyroid fed dogs with a total
sympathetic block resulted in a rise in the oxygen
consumption, heart rate, cardiac index, and ventri-
cular stroke work per unit of filling pressure which
was significantly greater than that seen during
their infusion in a comparable series of euthyroid
dogs. Whereas the infusion of l-adrenaline or
l-noradrenaline in euthyroid or thyroïd fed animals
resulted in equivalent inotropic, chronotropic or
calorigenic effects, there was a fundamental dif-
ference in the glycojenolytic effects of l-adrenaline
and of l-noradrenaline, as reflected in the blood
and serum concentrations of lactate, pyruvate,
and sugar. Whereas the infusion of l-adrenaline
consistently resulted in a rise in the serum lactate
and pyruvate and blood sugar, the infusion of
l-noradrenaline, despite its equal calorigenic effect,
produced a fall in the blood and serum concen-
trations of lactate, pyruvate, and sugar. The
normal values of the serum lactate and pyruvate
and of blood sugar observed in the thyroid fed
animals in the control state suggest that l-nora-
drenaline is the predominant mediator of the
physiological effects of thyrotoxicosis, as far as the
activity of the sympathetic nervous system is con-
cerned.

It was concluded that there is a dynamic inter-
relationship between the thyroid hormones on the
one hand and l-adrenaline and l-noradrenaline on
the other. The physiological effects of thyrotoxi-
cosis are not the result of the isolated action of
the thyroid hormones per se but are due to the
physiological effects of l-adrenaline and of
l-noradrenaline as augmented by the thyroid
hormones. Consideration of the work of others
and data from our laboratory indicates that
optimal concentrations of the adrenal cortical
steroids are essential for the dynamic activity of the
hormones of the thyroid and sympathetic nervous
system to be manifested.

This work has opened a new pathway for the
in vivo and in vitro investigation of the mechanism
of action of the thyroid hormones and of l-adrena-
line and of l-noradrenaline as they affect transfer
and utilization of energy for contraction in heart
muscle.

To study the mechanism of action of the above
hormones, the effects of temperature upon re-
action rates in heart muscle, as indicated by the
maximum rates of contraction and relaxation, have
been studied (Brewster et al., 1957). Using a
120-ohm bonded strain gauge arch sutured to the
right ventricle, the maximum rates of isometric
contraction and relaxation in g/second have been
observed and related to the contractile force of
ventricular muscle in euthyroid and hyperthyroid
dogs. The body and heart temperatures of the
above animals have been varied over the temperature 18°C to 43°C. This range spans fairly completely the temperatures at which the dog heart is capable of contracting and doing work. It was observed that the rate of contraction showed the smallest variation as a function of temperature. The Q10 (temperature coefficient of this rate process over a 10°C temperature range) varied from 1.2 to 1.3. The rate of relaxation showed the greatest variation as a function of temperature. The Q10 of the rate of relaxation varied from 4.3 to 4.6. The spontaneous heart rate (beat/min) and the total oxygen consumption of the animals varied as a function of temperature with Q10 coefficients varying from 2.10 to 2.70.

The Q10 of the rate of contraction indicates this phase of heart muscle activity to be a physical process not involving chemical bond energy or electron transfer. It is consistent with the view that contraction is the result of an ionic interaction between actin and myosin in which these molecules lose their charges and form the insoluble precipitate, actomyosin.

The Q10 of the rate of relaxation indicates this phase of activity in heart muscle as a phase requiring active transfer of chemical bond' or quantum energy to return the proteins, actin and myosin, to their extended, dissociated, and charged state. The rate of relaxation can be regarded as the rate of phosphate bond energy transfer. This is consistent with the view that in terms of the internal energy of the system, the contracted state is a low energy state while the extended or relaxed state is the charged high energy state. Contraction involves the decrease in free energy and the incidental performance of work. Relaxation is an active chemical process increasing the internal energy of the contractile protein system.

Focusing upon the rate of relaxation as a rate process indicating energy transfer, it has been found that adrenaline and noradrenaline, when injected in physiological concentrations, primarily increase the rate of relaxation of heart muscle. It is postulated that the increase in contractile force of heart muscle produced by adrenaline and noradrenaline may be due to their augmentation, directly or indirectly, of quantum energy transfer to the contractile proteins. (This is consistent with the high oxidation reduction potential of adrenaline.) The thyroid hormones have been found to have no effect upon the rate of relaxation or upon energy transfer in the absence of adrenaline and noradrenaline. Their activity in the presence of the sympatho-adrenal hormones can be explained by considering thyroxine and triiodothyronine, both amino acids, active only when incorporated into the polypeptides actin and myosin. In these proteins, their heavy iodine ions can serve as localizers of electron charge density. As such, they would increase total coulomb repulsive forces between charged points in the protein molecule. This factor would both increase the rate of dissociation of actin and myosin and increase the internal energy of the dissociated system.

It has also been observed that when the "contractility" of heart muscle is depressed by anoxia, anaesthetic agents, or by increased blood carbon dioxide tension, the primary characteristic of depression is a parallel decrease in contractile force and rate of relaxation. This has raised the possibility, to be thoroughly investigated, that the primary effect of an anaesthetic agent is to block the transfer of energy from high energy phosphate bonds to the contractile proteins.

This work is being continued and extended by Dr. Brewster.

**SUBJECTIVE RESPONSES**

For a decade my own work has been largely directed to this area. It is probable that pain is the first problem the physician was asked to treat. It is also probable that, because of its antiquity, it has gathered about it more folk lore than any other medical problem. My own special interest in investigation has been to try to cut through the false problems to the real ones by the application of quantitative methods in the elusive field of subjective responses, in short to measure the effects of drugs on pain. This problem is broader than pain alone and I have long considered that this work on pain is a prototype for the quantitative study of subjective responses in general.

The material we use is largely severe postoperative wound pain. An important question is, how representative are the conclusions one can draw from this material, how broadly can one's conclusions be applied to pain problems in general?
A reassuring answer is shown by the remarkably close checks between our findings as compared with those of Houde and Wallenstein at the Sloan Kettering Laboratory. They studied chiefly pain arising from metastatic cancer. The agreement of the two independent laboratories using different pain sources was as exact as the agreement from time to time within a given laboratory for pain from one source (Beecher, 1957).

The methods we use and the controls involved have been described (Denton and Beecher, 1949; Keats et al., 1950; Beecher, 1952a, b, 1953, 1957) in detail elsewhere. Briefly, the procedure is to take 25 or more individuals in severe postoperative pain, set up standards of partial and complete relief, administer drugs in a random fashion, using the “double unknowns” technique wherein neither the subject nor the observer is aware of what was used, insert placebos also as unknowns, use “correlated” or “cross-over” material (all subjects receive all agents), and validate mathematically supposed differences. When these essential controls are employed one can work within a 10 per cent error. The accuracy involved in dealing with the effects of drugs on subjective responses is as great as when one deals with objective measurements of therapeutic effects in man.

One reason why this work has seemed particularly interesting is that the results are useful in two areas, the theoretical and the practical. For example, the rapid flattening of the dose-effect curve, the rapid achievement of a ceiling effect, on increasing the dose of morphine, say, indicates that the optimal dose of morphine per 70 kg of body weight is 10 mg (Lasagna and Beecher, 1954a), for increase of the dose to 15 mg adds little to the pain relief but does seriously increase the side effects to a point approaching undesirability. This brings to the fore a problem of definition wherein we must recognize that to appraise pain relieving agents two scales of values must be taken into account: (a) side effects per mg and (b) pain relief achieved per mg; classically, this would be called potency; to use this definition of potency alone would be most confusing, for example, one would say that pethidine is as potent as morphine. A somewhat surprising finding on the quantitative techniques mentioned is that 50 mg pethidine equals 10 mg morphine in pain-relieving power (Lasagna and Beecher, 1954b).

It must be made clear that while it is easy to speak of side effects, it is difficult to be certain that one evaluates them properly. There are a number of reasons why pain must usually be studied as it arises in disease, rather than to depend on pain experimentally produced, if one’s purpose is the appraisal of analgesic agents. These matters have been discussed in a long review (Beecher, 1957). The difficulty is that when one employs, as is usual for this purpose, pain arising in disease, the disease itself often carries with it symptoms like those produced also by the agents in question—nausea, for example—and it is difficult or impossible to get at the exact truth. On the other hand, the use of normal subjects is not entirely satisfactory either, for it is not possible to be sure that morphine would not produce less nausea in the individual who was distracted by the pain and worry of his disease. Clearly, conclusions in this area must be guarded.

On the surface of the matter, the subject of side effects is rather prosaic, even dull; but I hope I can show that there is something exciting to be found here too. The principal physical side effects of narcotics, respiratory depression, vomiting, constipation, are well known and easily measured. On the mental and physical side combined there is addiction. (This is far outside my field of competence and will not be dealt with here.) Of the “mental” or subjective side effects there is nausea, and we have worked out techniques for measuring this (Knapp and Beecher, 1956); then there is “mental clouding” or confusion for which we have recently been obliged largely to develop our own psychological techniques in quantitative terms (Smith et al., 1957). Heretofore the confusion “mental clouding” produced by drugs has not been expressed quantitatively. The techniques we have evolved for measurement of mental clouding are broadly applicable to many problems, for example, to study the enormous new field of the so-called tranquilizers.

To return to the question of other practical advances, there are the data on comparative doses
of common analgesic agents, referred to in the case of pethidine. There is the demonstration that codeine, even in 60 mg dose or larger, administered parenterally, never achieves the pain relieving power of 10 mg morphine, but codeine does have, at 60 mg, side effects practically identical with those of 10 mg morphine, except for addiction liability (Lasagna and Beecher, 1954b). There is the recent finding (Gravenstein et al., 1956) that dihydrocodeine in 30 mg dose is a very powerful analgesic, although not quite so powerful as morphine, but, remarkably, it has no more side effects than a placebo, in the 30 mg dose. This is the first time a really powerful analgesic has been found that is not associated with severe depression of the respiration, frequent nausea and mental clouding. It marks a milestone in the long road to improvement of narcotic agents.

On the "basic science" side the mechanism of action and the site of action of drugs have long been of interest and some progress has been made in getting at these matters. As long ago as 1895, Strong, stimulated by a book written by Marshall the year before, postulated that suffering consists of two parts, the original sensation and the psychological reaction to that sensation. The concept is probably a very old one, for Voltaire commented in 1768 that there is no such thing as a sensation without a thought about that sensation. As we pass through life, there is a conditioning of familiar sensations. We have been able to support Strong's hypothesis with data which indicate that one site (and probably the principal one) for the action of drugs which modify subjective responses is the psychological reaction or processing component.

In the first place, there is reason to doubt that analgesic agents have power to modify the "original sensation". Fifteen groups have now failed to confirm the reports of Hardy et al. (1952) and others who use pain of experimental origin, and who have failed to confirm that the pain threshold is dependably responsive to the action of such agents (Beecher 1956a, 1957). This is negative evidence. It should be explained that the experimentalists such as Hardy et al. (1952) hold that the pain threshold measures the "original sensation".

On the positive side there is much evidence that factors which could not conceivably affect the pain apparatus in a drug-like way yet can be of dominating importance, presumably through altering the psychological reaction component. For example, there is the powerful placebo (Beecher, 1955b). We have been able to show in seven of our own studies and in eight from other laboratories, involving over a thousand subjects, that placebos have an average effectiveness of 35 per cent ± 2.2. When it is recalled that even a large dose of morphine, 15 mg, satisfactorily relieves (as defined) only 75 per cent of subjects in severe pain, it can be seen that the placebo accounts for nearly half of the possible drug effectiveness. It has been possible to present evidence when the stress is severe that the effectiveness of placebos is greater than this. Thus it was shown (Beecher, 1956b) when the pain is most severe that placebos account for 77 per cent of the effectiveness of the analgesic (10 mg morphine).

In a still different type of study further evidence was obtained for the importance of the reaction component. Wounded soldiers (Beecher, 1946) who are clear mentally, not in shock and who have had no analgesics at all in many cases and in no case within 4 hours, have enough pain to want anything done about it in only 25 per cent of the cases. Civilians having much less tissue trauma as a result of surgical procedures than the soldiers, have enough pain to want pain relief in over 80 per cent of the cases. This cannot be explained on the basis of familiarity with narcotic agents on the part of the civilians, for the same high percentage held whether the surgery was necessary because of long illness, as with cup arthroplasty, or whether it was required by fresh fracture of bone. The explanation appears to lie in the significance of the wounds: the soldiers, most of whom were studied on the Anzio beachhead where imminent death seemed likely, considered their wounds to be a ticket home. The war was over for them. They were not unhappy with their lot. To the average civilian the necessity for surgery is a calamity. The significance of the wound seems to determine the suffering experienced. These examples provide
evidence that factors which affect the psychic reaction component can dominate the pain experience (Beecher, 1956c) and thus provide evidence for the first time that Strong's 62-year-old hypothesis is correct.

The techniques which have been described in some detail have been applied to other problems, especially to a quantitative study of changes in mood produced by drugs (Lasagna et al., 1955; von Felsinger et al., 1955). They have been applied to cough (Gravenstein et al., 1954). They are being applied as already mentioned, to measuring the "mental clouding" produced by narcotic drugs (Smith et al., 1957) and to a study of itch (Macris and Beecher, 1957).

CONCLUSION

In the 21 years of existence of the Anaesthesia Laboratory some 200 papers have been published from it. No attempt has been made to review all of this work, but, rather, typical examples have been presented in order to give some idea of the kinds of problems we have found of interest. We believe that useful contributions to knowledge have been made in the course of this work: but however that may be, we are firmly of the opinion that a direct consequence of these painstaking enquiries is better teaching, with the incultation of a critical, but not destructively critical, attitude on the part of those we have trained. We believe that the development of such an attitude is essential for the long range and sound development of our specialty.

Experimentation in animals has given rise in the past to very great discoveries; it will in the future. Without in the least minimizing the importance of animal experimentation now or in the future, it is fair to point out that there is rightly an increasing interest in human physiology and in human pharmacology. It is clear when one studies the effects of the central nervous system depressants, that man has become the medium for much of such work.

In the studies described in the preceding pages new questions have been asked; some have been answered; but only the surface of an area has been scratched which can have great importance in the development of medicine. It needs long range planning. It needs long range support.

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CORRESPONDENCE

IRREVERSIBLE CURARIZATION

Sir,—May I express my disagreement with Dr. Burchell. At the conclusion of his only too topical article on irreversible curarization (*Brit. J. Anaesth.*, 1957, 29, 127) he recommends that “until the aetiology has definitely been established, all routine drugs must be tried”.

For several years I have been teaching that this is exactly what one must not do. Apnoea persisting at the end of operation may be due to such a number of different causes that there can be no specific treatment. Any symptomatic treatment may well be ineffectual and can often be dangerous. I am convinced that in many of these cases which end fatally, the cause of death is not the apnoea but the treatment directed at the patient in impatience, misguided attempts to restart spontaneous respiration—dangerously large doses of neostigmine, powerful medullary stimulants such as nikethamide, vigorous overventilation with an absorber in situ or alternately leaving the patient apnoeic for a minute or two—all measures calculated to impose a considerable strain on the fittest of subjects.

A frequent history is that at the end of operation “the patient was in a reasonably good condition and only began to go downhill subsequently when restorative measures were applied”. Dr. Burchell reported that his own patient was in “excellent” condition. I am convinced that the only safe way to treat these cases is to be patient, to maintain normal pulmonary ventilation, preferably with a mixture of about 5 litres nitrous oxide and 3 litres of oxygen without an absorber, and to direct all one’s efforts at diagnosing and then removing the particular underlying cause. Until the latter has been established, patience must be the watchword and drugs must be withheld. Apnoea is not of itself lethal, and correctly treated apnoeic patients can survive almost indefinitely. Correct treatment however, does not include the hopeful, indiscriminate administration of a variety of potent drugs.

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