Pain is the arch enemy of mankind. To escape its ravages, to achieve a surcease from its devastating blows, man has ransacked the entire world to obtain drugs that would obliterate pain. This has been a universal quest of mankind, for pain is a tax that is levied on everyone for the privilege of life on this planet. Some are taxed lightly, others are taxed heavily, but all are taxed. In “Paradise Lost” Milton declared, “Pain is perfect misery, the worst of evils, and excessive, overturns all patience.”

Physiologically, pain is a specific sensory experience which is mediated through nerve structures which are separate from those which mediate other sensations, such as touch, pressure, heat, and cold. Pain is recognized as a warning signal of danger to the organism. Since the awareness of pain is dependent upon consciousness, it follows that the obliteration of consciousness will cause the complete abolition of pain. Through a long history of the use of opium, mandragora, and alcohol to quell the pain of surgical trauma, man discovered the use of the volatile anesthetics during the decade 1840–50. The names of Horace Wells, William T. G. Morton, Crawford W. Long, and James Y. Simpson are associated with this illustrious chapter in medical history. Until the turn of the century, the three anesthetics, nitrous oxide, ether, and chloroform were the principal agents in the physician’s armamentarium employed to produce surgical anesthesia. General anesthetics abolish the perception of nerve stimuli, produce a hiatus in consciousness, and obliterate motor activity. No class of drugs has contributed more to human welfare than the anesthetics. They have made modern surgery possible, and changed the operating room from a chamber of horrors to a place where the tranquility of unconsciousness supervenes.

Mechanism of Anesthetic Action

That the living cell can become the site of consciousness is perhaps the most baffling and yet intriguing problem in biology. An equally difficult and puzzling problem is the mechanism of action by which chemical compounds such as the volatile anesthetics, not metabolized by brain cells, can produce a hiatus in consciousness. Lillie stated the problem so cogently many years ago, “The problem of general anesthesia is a fact inseparable from the wider problem of the nature and conditions of irritability in general.”

The first major assault in the problem dates back to the turn of the century when Hans Horst Meyer and E. Overton expressed a theory of narcosis in the following postulates:

1. All chemically indifferent substances which are soluble in fats and fatlike bodies must exert a narcotic action on living protoplasm, insofar as they can be distributed in it.
2. The effect must manifest itself first, and most markedly, in those cells in which fatty or lipid substances predominate in the chemical structure and presumably in which they form essential participants in the cell function; viz., in nerve cells.
3. The relative efficiency of such narcotic agents must be dependent upon their mechanical affinity for lipid substances on one hand, and for the remaining body constituents, i.e., principally water, on the other hand. Their efficiency is therefore dependent upon their partition coefficient which determines their distribution in a mixture of water and lipid substances.

One is inclined to call these time-honored postulates a statement of narcotic distribution in the body rather than a theory of narcosis. However, when viewed with respect to our present knowledge of cellular respiration they represent a definite contribution which has withstood the pruning knife of time.

Our experience with the oil/water coefficients of newer anesthetic agents has been most gratifying. In general, we observed that the oil/water coefficients of many of the commonly used volatile anesthetics, could be plotted against the reciprocal of their water solubility. The latter physical constant is most readily measured and enables one to make a first approximation of the potency of an anesthetic agent (7).

Since anesthetic potency and oil/water coefficients vary with each other, and the oil/water coefficient varies with the insolvency in water, it follows that potency and the reciprocal of water solubility bear a direct relationship to each other (7).

The formulas of three generally used anesthetics namely nitrous oxide, ethyl ether, and cyclopropane show a wide variation in chemical constitution. One property in common, however, is a high oil/water coefficient. Some ten years ago we prepared cyclobutane and studied it pharmacologically and clinically as an anesthetic agent. Its properties were strikingly similar to those of cyclopropane. However, owing to the greater difficulty in synthesis the use of cyclobutane was abandoned. Cyclopentane, the next member in the series, which is inexpensive and enjoys a high oil/water coefficient elicited unconsciousness in dogs and monkeys with marked clonic convulsive seizures. Thus it appears that, although these volatile anesthetic agents enter and leave the brain unchanged, the cells of the brain are exquisitely sensitive to their chemical configurations.
Ferguson (2), in considering an interpretation of his data on the action of volatile anesthetic agents, pointed out that solubility, vapor pressure, oil/water coefficients, and adsorbability, were measures of the tendency of the agents to distribute between two phases. Further when equilibrium was established, the chemical potential would be the same in both phases. Brink and Posternak (4) contend that the work required in the transfer from the pure liquid to the narcotized cell is the same for all substances which produce equal degrees of narcosis at equal thermodynamic activities. They speculate that anesthetics probably produce their effect in the regions of the cell in which their molecules fit much as they fit into their own pure liquid phase. Wulf and Featherstone (4) consider these concepts consistent with their hypothesis, namely, that the increasing potency of clinical anesthetic agents parallels in general the van der Waals' constants. Based upon these data they were able to account for the anesthetic action of the inert gas Xenon. They point out that its anesthetic potency should be equivalent to that of nitrous oxide and ethylene, since the van der Waals’ constants are essentially the same. And it is true that Xenon, nitrous oxide, and ethylene do exhibit about the same degree of anesthetic potency.

These interesting studies of the physical properties of anesthetic agents have contributed much useful information to our knowledge. But the key to the problem lies in an understanding of what distortion of enzymic activity is provoked by their presence in the brain, which in turn is responsible for the hiatus in consciousness.

Many studies have been designed to pinpoint the specific enzyme system which is responsible for anesthetic action and the concomitant loss of consciousness. Numerous anesthetic agents have been shown to depress the oxygen uptake of brain brei. They exert little or no effect upon anaerobic glycolysis. It appears that in the process of the main line oxidation, anesthetics interfere with a sensitive flavoprotein which connects the phosphonucleotide dehydrogenase system with the cytochromes. The depression is reversible.

It has been shown that there are many ways in which an anesthetic agent can exert its effect upon cerebral enzyme systems and evoke unconsciousness. Furthermore, all of the generally used anesthetic agents do not achieve anesthesia by affecting the same target enzyme system. For example, Brody and Bain (5) demonstrated that barbiturates in anesthetic concentrations uncoupled oxidation from phosphorylation in the mitochondrial fraction of the rat’s brains. Hulme and Krantz (6) showed that diethyl ether produced a similar type of uncoupling of oxidation from phosphorylation.

Since the high energy phosphate bonds of adenosine triphosphate are necessary for the synthesis of acetylcholine, a diminution of the level of ATP would result in a paucity of acetylcholine essential for neuronal transmission. However, Xenon which may be classed as a volatile anesthetic, was shown by Featherstone and Levy (7) to be incapable of uncoupling oxidation from phosphorylation. Nitrous oxide likewise does not affect this enzyme system. Nevertheless, Hosein, et al. (8) demonstrated that nitrous oxide inhibits anaerobic glycolysis and also depresses certain facets of the hydrogen transport system.

Implicit in these statements is the fact that the precise mechanism of anesthesia at an enzyme level has not been delineated. The enzymic activities responsible for consciousness appear to be so complex and intricately interdependent that an agent influencing one segment of the system comcomitantly affects the harmonious function of the whole. In addition it seems likely that the anesthetic agents in use affect the enzymic activity of the brain at different links in the complex chain of consciousness.

In summary, it appears that our present knowledge permits the following generalizations:

1. The use of the Overton-Meyer theory as a statement of anesthetic distribution in the body.
2. The presence of the agent in the central nervous system attacks the “main line” oxidation in the cells of the central nervous system. The target enzymes for different anesthetics are not always the same.
3. Anesthetics have been shown to act on a flavoprotein connecting the phosphonucleotide dehydrogenases with the cytochromes. Certain agents uncouple oxidation from phosphorylation.
4. The enzymic inhibitions are reversible processes.

**Fluorine-Bearing Anesthetic Agents**

Halogen-bearing anesthetic agents have occupied an important place in the armamentarium of the anesthesiologist for many years. Thus chloroform and ethyl chloride were among the first volatile anesthetics employed. Tribromoethanol also has been extensively used. Within the last two decades the synthesis of many fluorinated hydrocarbons and ethers has prompted their use as anesthetic agents. Robbins (9) studied a large number of fluorinated and mixed halogenated hydrocarbons on animals; not many of these appeared to be suitable for human anesthesia. Lu, Ling, and Krantz (10) extended these studies and found trifluoroethyl vinyl ether (Fluoromar) suitable for anesthetizing man. This appears to be the first fluorinated volatile anesthetic to have been used on man and made available for clinical anesthesia. This was followed by the clinical application of 1,1,1-trifluoro-2,2-bromo-chlorethane (Fluothane) by Raventos (11). In our further studies with fluorinated ethers, it was observed that hexafluorodiethyl ether (Indoklon) elicited violent convulsive seizures upon inhalation. This prompted us to use the agent in the treatment of mental illness as a substitute for electroshock therapy (Krantz, Truitt, and Kurland) (12). Many thousands of such treatments have been given with gratifying results. Of more than passing interest is the observation that Indoklon, a convulsive ether, enjoys little oil solubility, whereas Fluoromar, an anesthetic ether has a high oil/water coefficient.

Thus advances in the practical application of the volatile anesthetics have been marked; indeed they have far outrun our theoretical concepts of their mechanism of action.
The Non-Narcotic Analgesics

The anesthetics obtund pain by the abolition of consciousness. The narcotic analgesics relieve pain by increasing the threshold to pain and diminishing the alarm reaction to recurring pain. This is frequently accompanied with altered mental acuity and the hazard of addiction. The non-narcotic analgesics obtund pain without interference with mental acuity and present no addictive hazard.

The final stage of testing drugs at the Sloan-Kettering Institute is their use in treating cancer patients.

The non-narcotic analgesics are usually not effective in the relief of deep-seated visceral pain. They are not efficacious in affording relief from excruciating, sharp, and intense pain. However, they find a wide field of usefulness and are most valuable in the relief of arthralgias, myalgias, neuralgias, cephalalgias, and integumental pain in general.

Although the mechanism of action of the commonly used non-narcotic analgesics has not been conclusively delineated, certain evidence points to a tentative hypothesis for their use as analgesic drugs. Since these drugs do not interfere with the cortical activity of the brain by interference with mental acuity, it is likely that their action is mediated at a subcortical level. They appear to interfere with pain impulses carried over the lateral spinothalamic tract, raising the threshold of stimuli relayed from the thalamus to the sensory areas of the cerebral cortex. With the relief of pain mediated through the action of morphine or other narcotic analgesics, the tranquilizing of the patient and the suppression of the alarm reaction often persists longer than the increase of the threshold to pain. With this type of analgesia a second noxious stimulus reaching the sensorium is acutely recognized. With analgesia produced by the non-narcotic analgesics, additional noxious stimuli are not perceived owing to the blockade of the pain pathway below the sensorium.

The first and now most generally used agents in the class of non-narcotic analgesics are the salicylates and their derivatives. Salicylic acid was isolated from salicin by Piria in 1838. Sodium salicylate was used in medicine for the first time by Buss in 1875. Augmenting sodium salicylate in the field of analgesia in the decade 1880–90 came acetanilid, acetylphenetidin, and antipyrine. At the turn of the century Dresser synthesized acetylsalicylic acid which was called aspirin from the German word "Spirsaure" which is the German word for salicylic acid.

That aspirin occupies a place of pre-eminence in the field of non-narcotic analgesics is evidenced by the fact that the American public consumes it, in its various dosage forms, to the extent of 21 tons daily. In addition to the use of low dosage levels of aspirin for headaches and minor neuralgic pain, aspirin does not suffer in comparison with ACTH and cortico-steroid therapy in rheumatic fever and the various arthritides. Besides its analgesic and antipyretic actions, Reid (19) demonstrated that salicylates served as a primary metabolic stimulant (13). The pulmonary ventilation increase which is elicited by large doses of salicylates appears to be a response to the demand for a greater utilization of oxygen in the periphery. It is possible that the antirheumatic action of aspirin is associated with its peripheral metabolic stimulating action.

New additions to this class of analgesics have been few. The well-established mixtures of aspirin, phenacetin, and caffeine, APC, are abundantly used and within their field of usefulness appear to be effective. Salicylamide does not offer any advantage over aspirin. Furthermore it has not been established that acetopara aminophenol (APAP) is superior to acetophenetidin. Undoubtedly the most dependable and potent of the non-narcotic analgesics is aminopyrine. Unfortunately this compound has been incriminated in the production of blood dyscrasias and its indiscriminate sale in this country is prohibited. However, this condition does not prevail in many countries in Europe and aminopyrine is extensively used for the relief of pain. It appears to this observer that the evidence against the use of this potent analgesic should be re-investigated and its validity assessed by further controlled clinical studies.

More recent additions to the non-narcotic analgesics are Darvon (Lilly) and Zactirin (Wyatt). Darvon is 1,α-α-4-dimethyl-α-methyl-3-2-methyl 1-2-butanol propionate hydrochloride and Zactirin is ethoheptazine citrate. Each drug has a wide margin of safety and offers no addictive hazard. Reports from various sources are somewhat conflicting regarding the analgesic action of each of these drugs. However, reports indicate that Darvon is as potent as codeine as an analgesic. The fact that many of their dosage forms contain aspirin begets the critical evaluation of these newer analgesics.

Progress in both fields covered by this discussion, namely the volatile anesthetics and non-narcotic analgesics, has been marked. Flexibility in general anesthesia has been increased and anesthetic mortality materially reduced. The non-narcotic analgesics serve well within their field of usefulness. But there is much room for progress. Perhaps with the newer chemical structures leaving the assembly line of the organic chemist, and a more critical evaluation of them as analgesics by the pharmacologist and clinician someday we shall fulfill the Scripture's prophesy, "Neither shall there by any more pain."
Literature Cited