

Reports of Scientific Meetings

Ellis N. Cohen, M.D., Editor

Seventy-third Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics

The Seventy-third Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics was held in Houston, Texas, March 9-10, 1972. A major goal of this society is to encourage and evaluate clinical pharmacologic research in man. Although research in animals provides valuable data, final answers must eventually be obtained from man. Reflecting this need, the panel discussions were primarily concerned with means to secure more data from patients receiving drugs.

The keynote lecture, "Hypertension, A Controllable Disease," by Dr. Edward D. Freis, who received the Eighteenth Oscar B. Hunter Memorial Award in Therapeutics, opened the program and indicated its principal direction. Many papers were concerned with cardiovascular drugs, mainly antihypertensive and antiarrhythmic drugs. New antihypertensive agents, SKF 24260 and Minoxidil, were reported by B. R. Walker and C. Limas to be effective in the treatment of severe hypertension. Clonidine and methyldopa were reported by W. Mroczek to be equally effective in the treatment of hypertension when used in combination with the diuretic, chlorthalidone. Although well controlled, these studies included only a few patients. They were, therefore, unable to conclude whether these new agents were more effective than other commonly used antihypertensive drugs such as reserpine. Unhappy with current drug therapy, G. Onesti reported successful treatment of five patients with severe essential hypertension with stimulating electrodes chronically implanted around the carotid sinus. Stimulation of the carotid sinus was regulated by the patient. Five presentations discussed beta-adrenergic blocking agents; three in the treatment of hypertension and two in the treatment of cardiac arrhythmias. E. D. Freis reported the successful treatment of six mild-hyper-

tensive patients with a new beta-adrenergic blocking agent, MK-950. However, these clinical results appeared to be no different from the successful treatment of hypertensive patients with propranolol and practolol, as discussed in separate reports by E. D. Frohlich and R. C. Tarazi. Another new beta-adrenergic blocking agent, UK 6558-01, was reported by W. S. Aronow to reduce significantly the number of digitalis-induced arrhythmias in 16 of 19 patients studied. Still another potential use of propranolol was reported by R. Martz in the antagonism of marijuana-induced tachycardia. All of these studies suggest that we are likely to see preoperative patients receiving a variety of new antihypertensive drugs, including several beta-adrenergic blockers.

Although the majority of the studies were well controlled, most did not include enough patients to establish clearly which drugs are most effective with the fewest adverse effects. One panel addressed itself in part to this problem under the general title of "Computers in Support of Pharmacologic Research." H. Jick, using his experience as Director of the Boston Collaborative Drug Surveillance Program, suggested that the more subtle advantages and side-effects of drugs cannot be detected by observations of small numbers of patients. The majority of studies presented at this meeting were of this type. Large, intensive drug-surveillance programs, with strong computer backing involving several clinics, are more likely to detect drug superiority and adverse drug reactions.

Although P. Cole reported oral diphenylhydantoin to be ineffective in decreasing the frequency of premature ventricular contractions, D. W. Romhilt found the intramuscular administration of bretylium tosylate to be effective in six of eight patients. Once again, the small number of patients studied precludes comparison of these compounds with such useful drugs as quinidine and procainamide. Dopamine continues to be encouraging in the pharmacologic treatment of shock and cardiac

failure because of its positive inotropic effect on the heart, without producing a corresponding increase in myocardial oxygen consumption. L. L. Priano reported a positive inotropic and chronotropic cardiac effect in dogs with Etoxadrol, a new dissociative anesthetic agent.

One of the three papers concerned with levodopa therapy was presented by R. Johnston, who observed marked increases in blood pressure and temperature and reduction in MAC in dogs given levodopa acutely. However, chronic administration resulted in variable changes in MAC, suggesting no anesthetic difficulties in patients receiving levodopa chronically.

The last session was a joint program with the Association of University Anesthetists. J. W. Bellville reported an expected longer duration of obstetric caudal anesthesia when epinephrine was added to mepivacaine in a double-blind randomized study. Patients who received mepivacaine with epinephrine, however, had a longer first stage of labor than those who received mepivacaine alone. Three of the papers were concerned with muscle relaxants. R. D. Miller reported that more neostigmine is needed to antagonize neuromuscular blockade produced by gallamine than by either *d*-tubocurarine or pancuronium. However, the work of E. K. Zsigmond suggested that neostigmine should be replaced by pyridostigmine as an antagonist to nondepolarizing muscle relaxants because of its longer action and lesser muscarinic stimulation. As in studies reported previously, D. E. Longnecker found a positive chronotropic effect of gallamine in patients undergoing cardiopulmonary bypass.

Because the American Society for Clinical Pharmacology and Therapeutics is devoted to studies of pharmacologic problems in man, they and anesthesiologists should share many common interests and could both benefit from additional combined meetings and interactions in their pursuit of many common objectives.

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Ninth Annual Postgraduate Seminar in Anesthesiology

The "Mother and Newborn" was the topic of the Ninth Annual Postgraduate Seminar in Anesthesiology, held in Miami Beach, January 6-9, 1971. Participants included a distinguished group of anesthesiologists, obstetricians, and perinatologists. The plan of the meeting was to review concepts related to obstetric anesthesia rather than to stress the presentation of new material. The prerequisites of good obstetric anesthetic care were defined by H. Mendenhall to include understanding of: a) physiologic changes in pregnancy and the ways in which these alter the response to anesthesia; b) effects of anesthesia on normal processes of labor and delivery; c) factors which determine the response of the fetus to anesthesia in areas important to his adaptation to neonatal life.

PHYSIOLOGY OF PREGNANCY AND THE RESPONSE TO ANESTHESIA

The normal cardiovascular and respiratory changes of pregnancy, labor, and delivery were described by J. Bonica. He stressed the relationship between these changes and the pathophysiology and treatment of the supine hypotensive syndrome. Of particular interest is the use of the Colon-Morales apparatus, shown to be effective in obtaining left uterine displacement during cesarean section. G. Marx reviewed obstetric conditions associated with high risks of hypotension, and emphasized changes in labor and delivery which predispose to vomiting and possible aspiration during general anesthesia.

B. Smith discussed the use of inhalation anesthesia and analgesia. General anesthesia with intubation of the trachea now appears to be in widespread use. Most inhalation agents, when used in analgesic concentrations (0.3 to 0.4 MAC), do not seem to increase the incidence of infants with low Apgar scores.

LABOR AND DELIVERY

Several presentations dealt with the effects of anesthesia on the normal process of labor and delivery. E. Munson reported that analgesic concentrations of many gaseous agents,

including the new drugs *É*thane and Forane, are myometrial depressants, and their effects are dose-related. One exception may be cyclopropane, since some studies suggest that it induces increased uterine tone.

In a discussion of regional anesthesia, S. Shnider pointed out the importance of instituting anesthesia only after labor is well established to avoid slowing labor. He also suggested that 0.6 per cent epinephrine, added to a local anesthetic, may be sufficient to decrease uterine contractility. He reported a relatively high incidence (24 per cent) of fetal bradycardia following paracervical block with 1 per cent lidocaine or carbocaine. In contrast, the incidence of bradycardia was significantly less with prilocaine. Some participants believed satisfactory paracervical block could readily be achieved with a 0.5 per cent solution. Others recommended cautious use of local anesthetics in patients with acidotic fetuses.

J. Bonica dealt with the controversial use of halothane in obstetrics. Its effect on the uterus makes it useful when uterine relaxation is desired; *i.e.*, breech deliveries, internal or external version, or manual removal of the placenta. He suggested, however, that this same property, and the drug's poor analgesic qualities at low concentrations, make it unsuitable for normal vaginal deliveries or for cesarean section.

THE FETUS

M. Finster reviewed factors which regulate the placental transfer of drugs. He mentioned two considerations which interfere with predictions of the amount of drug transferred across the placenta and reaching the fetal brain. One factor is the pattern of blood flow and distribution of cardiac output peculiar to the fetus. The other is absorption of drugs from umbilical vein blood as it passes from the placenta through the liver.

G. Levinson commented on recent experiences with several intravenous agents. Although diazepam rapidly crosses the placenta, it did not produce neonatal respiratory depression, as judged by Apgar scores and acid-base measurements. The drug may benefit by reducing local anesthetic toxicity and narcotic

requirements. However, diazepam appears to produce some neonatal hypoactivity and hypotonicity which may persist through the first day of life. Innovar has been used primarily as a supplement to regional anesthesia during the second stage of labor for cesarean section and following delivery. Although neurolept-analgesia can provide satisfactory analgesia for forceps deliveries with minimal maternal circulatory changes, respiratory depression of the infant is not uncommon. Droperidol, when used without a narcotic, does not appear to produce fetal depression, as evidenced by Apgar scores. Ketamine has been used as the sole anesthetic agent for complicated vaginal deliveries, as an adjunct to nitrous oxide analgesia, and for the induction and maintenance of general anesthesia for cesarean section. In animal studies, increased arterial blood pressure produced by ketamine was associated with a comparable increase in uterine blood flow. Ketamine crosses the placenta rapidly, and preliminary data indicate that it can produce severely depressed infants. In some instances, mechanical ventilation of the infant has been difficult because of excessive muscle tone. As an induction agent, the drug does not appear to offer more than other induction agents.

Several presentations dealt with fetal distress, its etiology, diagnosis, and management. According to D. Caton, the most remarkable feature of the normal intrauterine environment is its stability. Stability is achieved, despite growing fetal demands, by functional and anatomic development of the uterus and placenta. Inadequate development of several mechanisms may reduce the margin of safety that the fetus normally enjoys. W. Spellacy described two biochemical analyses of amniotic fluid which have been useful during the last trimester in the management of patients with "high-risk pregnancies." Falling levels of the placental enzyme, HPL, suggest the onset of fetal deterioration and have been used as a guide to early interruption of pregnancy. Relative levels of lecithin and sphingomyelin in amniotic fluid have been found to relate to the degree of maturation of mechanisms which produce pulmonary surfactant. The levels of these two compounds serve to gauge

when the infant lung is mature enough to withstand premature delivery without developing respiratory distress syndrome. E. Hon and H. Cohen discussed the rationale and use of fetal heart-rate monitoring and fetal scalp-blood sampling for the diagnosis and management of fetal distress during labor.

MEMORIAL LECTURE

The Jose E. Usubiaga memorial lecture, "Respiratory Distress Syndrome—Current Status," was delivered by L. S. James. He reviewed the history of the disease, including the work of Adams, who characterized the syndrome as one involving a number of organ systems in which there is a failure to adapt to extra-uterine life. Immaturity appears to be the most important predisposing factor. The syndrome is associated with the deficiency or absence of a pulmonary surface agent produced by type II cells in the alveoli. It is now possible to predict, with some degree of certainty, which infants are likely to develop the syndrome, through prenatal analysis of lecithin and sphingomyelin in amniotic fluid.

MECHANICAL VENTILATION OF THE NEWBORN

J. Downs discussed the characteristics of an "ideal" ventilator. All ventilators should be equipped with airway pressure and inspired oxygen concentration alarm systems, variable minimum and maximum pressure limit settings, and an inspired-gas temperature sensor alarm. They should be able to provide continuous positive-pressure ventilation (CPPV), a technique which appears to improve intrapulmonary mixing of gas, to increase FRC,

and to decrease the alveolar-arterial oxygen tension difference. G. A. Gregory stated that arterial oxygen tensions tend to increase with CPPV, permitting reduced inspired oxygen concentrations and reduced likelihood of pulmonary oxygen toxicity. L. Stern reported encouraging results in severe respiratory distress syndrome, which was resistant to either negative-pressure ventilation or positive-pressure ventilation. He utilized a combination of intermittent positive-pressure ventilation and constant negative extrathoracic chest-wall pressure, with striking improvement in arterial blood gases where previous attempts have been unsuccessful. P. R. Sawyer discussed a new method of oronasal mask ventilation and showed that its early application significantly decreased the number of distressed infants needing intubation, although mortality was not improved.

L. Stern emphasized that the success or failure of mechanical ventilation is largely dependent upon personnel and not equipment. Recent studies of small, premature infants suggest a risk of vasoconstriction of the retinal vessels with Pa_{O_2} levels as low as 100 torr. The need for constant and frequent monitoring of arterial gases during the course of mechanical ventilation assumes even greater importance than that already ascribed to it.

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The Anesthesiologist's Bookshelf

Edited by MEREL H. HARMEL

The Pathophysiology and Treatment of Drowning and Near-drowning. BY JEROME H. MODEL. Springfield, Ill., Charles C Thomas, 1971. Pp. 119. \$9.50.

Although no single disease kills as many healthy young people each year as drowning, medical texts

take little notice of the subject. This monograph by Dr. Modell is the first attempt to present a detailed statement of current knowledge of this common form of accidental death. Certainly this insures attention from anyone with a concern for management of emergency medical problems.