CHEST PERSISTED FOR SEVERAL DAYS. DURING THE TEST THE BLOOD-PRESSURE ROSE FROM 130/80 MM. TO 200/140 MM. Hg in five minutes, and the pulse-rate increased considerably. These effects were attributed largely to fear and asphyxia rather than to a direct effect of the d-tubocurarine chloride on the cardiovascular system, because the blood-pressure returned to normal in ten minutes. Electrocardiograms taken before the administration of the drug and three and ten minutes after its administration showed no abnormality. No undesirable after-effects were observed. No analgesic action was observed with a dose of 30 mg. of d-tubocurarine chloride.

"Further tests were then made on the conscious subject to determine the method of administration of the drug likely to give the most prolonged degree of relaxation. The administration of fractional doses was tried first. . . . We . . . decided that, owing to rapid destruction and elimination, the administration of a given dose by a drip transfusion was not the best way of giving it. . . . A dose of 15 mg. of d-tubocurarine was injected intravenously, and then a similar dose intramuscularly. The effects produced were similar to those obtained with 20 mg. given intravenously in a single injection, but they lasted much longer. . . . It was therefore decided that the best method of administering d-tubocurarine chloride during surgical operations was to begin with an adequate curarising dose intravenously and to reinforce this with a further quantity given intramuscularly if the operation was likely to last for more than from forty to forty-five minutes. When supplemented by gas-and-oxygen anaesthesia the relaxing effect of an optimal dose of d-tubocurarine chloride is prolonged for approximately this period. . . . Clinical trials with d-tubocurarine chloride were undertaken (1) to determine the preliminary dose necessary to produce muscular relaxation sufficient for abdominal surgery, using "Pentothal"-gas-oxygen second-plane anaesthesia; (2) to find what further amounts were needed to maintain relaxation for so long as the operation lasted; and (3) to compare patients who had had the drug with similar patients in whom relaxation had been obtained by other anaesthetic agents, and to observe any complications in using the drug either during operation or postoperatively. In all, 180 cases were observed. . . .

"Perfect relaxation for abdominal operations was obtained by administering a dose of 2–2.5 mg. intravenously per stone of body-weight after the patient had been stabilized with pentothal and gas-and-oxygen in second-plane anaesthesia. The dose is a critical one and, if not carefully selected, may lead to respiratory depression. . . . The chief complication experienced was respiratory depression or even arrest. . . . Special care is needed when giving the drug to patients in the Trendelenburg position. Apart from respiratory depression, complications and difficulties during operation were few. Postoperative complications were less than after spinal and general inhalation anaesthesia. The chief advantages of d-tubocurarine chloride as an adjunct to anaesthesia are the ease of administration, the profound relaxation, the freedom from shock, the rapid postanaesthetic recovery, and the low incidence of postoperative complications." 13 references.

J. C. M. C.


"The increasing use of curare (Intocostrin) as an adjunct to anaesthesia and for other clinical purposes indi-
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cates the need for additional information regarding its action in the body. . . . Intocostrin is reported by the manufacturers to owe its curare action (interference with the passage of impulses from motor nerves to skeletal muscles at the neuromuscular junction) almost entirely to its content of \( \text{d-tubocurarine} \), an alkaloid found in Amazonian curare. This alkaloid has been crystallized and its chemical structure established fairly completely. It is less potent than curarine, the characteristic alkaloid of curare from British Guiana. . . . Intocostrin (from 0.5 to 10.0 units per kilogram) was administered to rats, mice, guinea pigs, rabbits, and cats subcutaneously, intramuscularly, intraperitoneally, or intravenously. For all injection routes, the drug was diluted if necessary to keep the volume at least 0.4 cc. The marginal ear veins of unanesthetized rabbits and the exposed femoral veins of rats were used for intravenous injections. The rats were lightly anesthetized with ether for the exposure of the veins and were allowed to recover to the point of moving spontaneously before the intocostrin was injected. Practically all the injections were made rapidly (within two to five seconds); a few slow (from one to four minutes) intravenous injections into rabbits indicated that the rate of injection did not make a significant difference in the effects. Crystalline \( \text{d-tubocurarine} \) (6.17 standard intocostrin units per milligram) was dissolved in Ringer's solution and administered in suitable dilution by rapid subcutaneous or intramuscular injection to mice and to a few rats and guinea pigs (from 0.5 to 1.0 mg. per kilogram).

"Most of the experiments with intocostrin were done on rats (weighing from 150 to 200 grams). No difference in the susceptibility of the sexes was noted, but it was found that the amount of intocostrin required to kill the rats decreased as their stay in the labora-
tory was prolonged. The deciding factor in this effect was presumably either age or nutrition, but this was not determined. A homogeneous group of rats was used as far as possible for the sodium amytal series and its control. . . . Sodium amytal (from 75 to 100 mg. kilogram, intraperitoneally) was found to produce complete anesthesia in our rats without intocostrin. As the combination of this dose with intocostrin was usually fatal, sodium amytal was used at the minimum level (between 50 and 75 mg. per kilogram) that permitted the introduction of a hypodermic needle without causing the animal to withdraw its leg. Intocostrin (2 units per kilogram) was then injected subcutaneously or intramuscularly. In a few animals in the series, the sodium amytal was not injected until severe convulsions had developed following intocostrin injection. Oxygen, a mixture of 5 per cent \( \text{CO}_2 \) and 95 per cent \( \text{O}_2 \), or cyclopropane, when used, was delivered at a rate of 1,000 cc. per minute by an anesthesia gas machine into a 2 liter jar in which a rat was placed. Cyclopropane was started in the proportion of 3 parts to 7 parts of oxygen and then was reduced to the concentration required to maintain light anesthesia. Artificial respiration was administered manually or by breathing into a tube placed over the animal's nose. \( \text{Neostigmine methyl sulfate} \) (from 0.5 to 0.75 cc. \( 1/4,000 \)) was injected intramuscularly into two rats. . . . Intocostrin or crystalline \( \text{d-tubocurarine chloride} \) injected in sufficient dosage . . . produces hyperexcitability and clonic convulsions in addition to partial curarization.

"Signs of central nervous stimulation are more conspicuous in some species than others and are shown by rats without signs of asphyxia. Species (rats, guinea pigs, mice) manifesting much stimulation are killed by smaller doses of the drug than species (rabbits, cats) manifesting more curarization.
With fatal doses, death in all these animals is due to asphyxia, attributed in part to curarization of respiratory neuromuscular junctions peripherally and in part to stimulation centrally. The asphyxia may be relieved by neostigmine (peripheral action) or by sodium amytal (central action). Sodium amytal protects 60 per cent of rats from the effects of a dose of intocorin (2 units per kilogram) fatal to 95 per cent of untreated rats. The other 40 per cent of rats given sodium amytal prior to intocorin live twice as long after the intocorin injection as those not given sodium amytal. Central nervous depressants (sodium amytal, cyclopropane), decrease, abolish, or prevent intocorin convulsions. Reduction of asphyxia by oxygen administration or artificial respiration is less, if at all, effective in controlling convulsions. The conclusion from these observations that central nervous stimulation is one of the pharmacodynamic actions of intocorin is in agreement with the conclusions of other workers using other curare preparations. The flaccidity and decrease of spontaneous movements manifested by mammals given intocorin or d-tubocurarine alone do not develop into complete neuromuscular paralysis until just before death. In animals given a central nervous depressant in addition to intocorin muscular relaxation becomes complete at an early stage of intocorin action. Certain central nervous system depressants may be useful adjuncts to intocorin to combat central stimulation as well as to increase muscular relaxation.” 18 references.

J. C. M. C.


"Brazier and Finesinger have shown with the aid of the electroencephalograph a depressant effect of pentothal sodium on the several parts of the cortex. First the frontal area was depressed, then the parietal and, last, the occipital. It has been demonstrated in vitro that barbiturates exert an inhibitory effect on cellular respiration of the brain, particularly in the parts of the brain with the highest oxygen intake, such as the more cephalic regions, which suffer the most pronounced metabolic retardation. . . . An opportunity to determine whether the cerebral hemispheres are depressed before other parts of the brain is made possible by the course of the cerebral venous return. If, for example, the administration of a drug reduces the arteriovenous oxygen difference of the blood from the side carrying the cortical component more than that from