Summary

A case of primary agranulocytosis in a man aged 30 is described, together with a method of treatment by continuous intramuscular drip pentose nucleotide. That recovery was probably spontaneous is discussed in the light of possible treatments.

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THE EFFECT OF *d*-TUBOCURARINE CHLORIDE ON SENSATION IN MAN

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Curare is being increasingly used as an adjunct to anaesthesia. It has been employed widely in America as a biologically standardized extract of curare known as "intocostin," prepared by E. R. Squibb and Sons. It is being used in this country as the active principle isolated by Harold King (1935), *d*-tubocurarine chloride, and is sold as "tubarine."

There seems to be a belief that curare itself has some central depressant action and may thus contribute an analgesic or anaesthetic action of its own when used in anaesthesia. Theoretically this might be possible, as curare is known to block the effect of acetylcholine at ganglia and at the neuromuscular junction; and recent work (Bülbring and Burn, 1941) suggests that acetylcholine is concerned in transmission in the central nervous system. However, experimental evidence on the effect of curare on the central nervous system is confusing.

Von Euler and Wahlund (1941) confirmed earlier reports of an initial central stimulant action on the vasomotor and respiratory centres after intracisternal injection of curare; prolonged action of larger doses caused paralysis of these centres. Intralumbar injection of curare had a strychnine-like effect on spinal reflex excitability. Fegler (1942) showed an initial stimulation of respiration due to curare in anaesthetized dogs, and this may have been central. Other workers (Kahlson and Peil, 1937, in rabbits, for example) obtained respiratory depression. A narcotic effect of curare was reported by Feitelberg and Pick (1942), who performed electroencephalography on frogs. Pick and Unna (1945) later showed that there were separate central and peripheral actions, the former being present when the frog could still jump. Ranyard West (Hartridge and West, 1931; West, 1935) claimed that curare has a "lissive" or rigidity-removing action on dogs in tetany by virtue of a central effect, since this action precedes paralysis of the animal. He also reports respiratory depression appearing before paralysis of the respiratory muscles.

Unconsciousness following the administration of curare to man is described by Whitacre and Fisher (1945), who claim that there was no clinical evidence of hypoxia in these patients, and that there was no period of analgesia preceding the sudden loss of consciousness and muscular paralysis. The two patients described were, however, exsanguinated and shocked. In a third patient, a 72-year-old woman, resection of the colon was performed, using premedication and 405 mg. of "intocostin." The patient was unconscious throughout. In two other patients curare in doses causing marked respiratory paralysis had no analgesic activity, the patients saying later that the pain was unbearable until cyclopropane was administered. Griffith (1945) mentions these results and concludes that, at least in safe doses, "curare is in no sense an anaesthetic agent." Prescott, Organe,

and Rowbotham (1946) made the same observation. Five minutes after the injection of 30 mg. of *d*-tubocurarine chloride the subject was just beginning to lose consciousness. At this time respiratory exchange was inadequate; the "resultant asphyxia was masked by the fact that the subject was breathing pure oxygen." They further report no analgesic action with this dose.

Other workers have claimed that curare enhances the narcotic effect of other drugs (Brody, 1945; Gray and Halton, 1946). Cullen (1944) and Gross and Cullen (1943) point out that ether, "avertin," and sodium thiopentone ("pentothal") have a curare-like action of their own, and this action may explain some of the supposed synergisms.

We have therefore obtained some information on a possible analgesic action of curarine (*d*-tubocurarine chloride, Burroughs Wellcome and Co.) given intravenously in doses which, though small (5 and 7.5 mg.), did cause noticeable weakness of the muscles of the eyes, face, and jaw, and, to a less degree, those of the neck and arms. The effect of each dose has been observed in two men each weighing 10 st. (63.5 kg.). Sensation and cerebation were tested before injection, five minutes later at the height of muscular weakness, and again at fifteen minutes after injection during recovery.

Sensation was tested as follows: touch, with von Frey's hair (0.5 g.); skin pain, with two needles mounted on von Frey's hairs, the heavier giving immediate pain with each prick and the lighter giving no immediate pain but only a delayed sting; deep pain, by pressure over the subcutaneous surface of the tibia with an analgesimeter, the reading in pounds pressure at which pain was felt being noted. Cerebation was tested by mental arithmetic and by the ability to repeat sentences read out by an observer.

After curarine no sensory changes could be detected by these simple tests. The pain threshold was unaltered—15 lb. (6.8 kg.) as against 13 lb. (5.9 kg.) before injection. Cerebation was also unimpaired. For an evaluation of the method the tests were later repeated on each subject after intravenous injection of morphine 1/6 gr. (11 mg.). This produced a definite rise in pain threshold, the analgesimeter readings rising from an average of 12 lb. to 24 lb. (5.4 to 10.8 kg.), and the response to the lightly mounted needle was much diminished, the sting alone being felt in one out of three pricks.

It appears, then, that in these doses *d*-tubocurarine chloride has no analgesic action, even at the height of muscular weakness.

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The campaign for wholesale immunization against diphtheria in Sweden was started in 1940, and in the period 1942-5 some two million doses were issued by the State bacteriological laboratory for this purpose. During the years between the two world wars, the incidence of diphtheria in Sweden was low, reaching a record low level in 1938 of only 107 cases. This comparative immunity has entailed a high and growing rate of non-immunes in the community, and in 1943 only 6.4% of 1,000 of Stockholm school-children were Schick-negative, but over 98% of school-children on receiving one dose became Schick-negative from being Schick-positive. Swedish practice now employs a single injection which, it is recognized, needs to be repeated after one and five years. The brevity of the immunity conferred by a single injection is emphasized by the observation that, a year and a half after a first injection, 57% of 600 children had in the interval again become Schick-positive while the remainder were still Schick-negative.

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