3164

Conditions under which subcutaneously injected epinephrine gives a hemodynamic effect.

ARNO B. LUCKHARDT and THEODORE KOPPÁNYI.

[*From the Hull Physiological Laboratory, The University of Chicago, Chicago, Ill.*]

The statements in the literature regarding the hemodynamic effects of epinephrine injected hypodermically are few and conflicting. Some investigators[1] report feeble pressor effects; others[2] are as certain that there is no effect unless perchance epinephrine is injected quite directly and accidentally into a small venule. Even those who report feeble positive effects (Meltzer and Auer) were probably mistaken in the facts and interpretation, as we will point out more specifically in our detailed report.

In the course of some work in which epinephrine was administered subcutaneously in dogs under light paraldehyde (and morphine) anesthesia an appreciable rise of blood pressure was noted during the 3 to 4 minutes following the injection. Repetition of the experiments yielded questionable results; for there was either no immediate rise in blood pressure following such injection or the progressive rise in blood pressure could be readily explained on the basis of recovery from the light paraldehyde anesthesia of the animals. However, it was soon noticed that gentle massage of the injected area effected an appreciable hemodynamic effect and this led to a systematic investigation of the phenomenon.

Four to twelve kg. dogs were used for the most part under light paraldehyde anesthesia (1 to 1.5 cc. per kg.) reinforced as found necessary by subcutaneous injections of morphine sulphate (¼ to ¾ gr.). Blood pressure records were taken from the carotid artery. Hypodermic injections of epinephrine were made

[1] Meltzer and Auer, *J. Exp. Med.*, 1905, vii, 59; *Zeit. f. Phys.*, 1905, xviii, 689. Foerster and Benkovics, *Zeit. f. ges. exp. Med.*, 1926, xlix, 1. Thiess, cited by Braun, Local Anesthesia, Lea & Febiger, 1914, 144. Goetsch, *Pa. Med. J.*, 1920, xxiii, 431, and others by same author between 1920 and 1922. Lyon, *J. Exp. Med.*, 1923, xxxviii, 655.

[2] Patta, *Archiv. di Farmac.*, 1905, iv, 329. Janeway, The Clinical Study of Blood Pressure, Appleton & Co., 1907, p. 223. Biedl, Innere Sekretion, Urban und Schwarzenberg, Wien and Berlin, 1913.

in a great many regions of the body in doses of ½ to 6 cc. (Parke Davis & Co.) in original dilution or more or less diluted with distilled water. In most instances the area so injected was gently or vigorously massaged immediately after injection and at various time intervals following injection. In a few instances the animals were injected subcutaneously from 12 to 19 hours prior to the massage.

Massage of areas injected with epinephrine was followed by a typical rise in blood pressure (15 to 180 mm. Hg.) secured with great regularity 15 to 17 seconds after the beginning of massage. The rise and fall of blood pressure are either abrupt and evanescent; or the fall may be gradual—the return to normal may take occasionally 10 to 15 minutes. In fact, the rise in pressure may be so protracted that the curve simulates the effect commonly seen after the first injection of pituitrin. The magnitude of the pressor response (with or without typical vagus action of medullary origin) depends in part on the dose of adrenalin injected but more particularly on:

1. *Time following injection.* Early after injection the response is likely to be poor or entirely absent, due to the local vasoconstriction of the injected area; for the effect elicited from a given area becomes more pronounced when the original intense vaso-constriction gives place to a dilatation of the subcutaneous vessels (secondary paralysis) or to hemorrhages into the necrosis of the skin (moist gangrene). Furthermore, by injecting small doses of $Na\,NO_2$ subcutaneously into the area into which the adrenalin is subsequently injected, local vasoconstriction is prevented and the rise of pressure on massage is immediate.

2. *The Type and Depth of the Anesthetic Used.* The lighter the anesthetic the more certain and the more pronounced is the response. Under deep morphine sulphate analgesia reinforced by ether for the purpose solely of preparing the animal for registration of the blood pressure, the response comes on very early and is quite pronounced. Paraldehyde anesthesia is the most serviceable because of the lightness of the anesthetic state and was most commonly used. Positive results were never obtained under barbital anesthesia (Barbital Sodium). The hemodynamic effect was also absent under paraldehyde in case this anesthetic was administered in doses which were excessive. The effect of massage was not due to a pressor response as a result of stimulation of

the sensory nerves made hyperexcitable by the subcutaneous injection of the adrenalin for (a) the reaction was delayed some 17 seconds, the rise was abrupt, and (b) stimulation of similar control area gives uniformly a depressor effect. The typical pronounced effect following massage could furthermore be abolished either by administration of ether (inhalation) or by the intravenous injection of small quantities of paraldehyde or barbital-sodium.

3. *The Fatigue or the Depression of the Peripheral End Organs.* (a) It was found early that the oft repeated massage of a given area is followed by a progressively weaker response. After ½ hour or more of rest massage of this area gave again the marked response. This fact can be variously interpreted. We have interpreted it provisionally as possibly indicating fatigue or depression of the peripheral end organs; for

(b) The pressor effect of intravenously injected epinephrine solution can be materially diminished by the intravenous injection of small amounts of ether.

There is no question that massage of a cutaneous area previously injected with epinephrine gives a pressor effect as a result of epinephrine reaching the general circulation, for (a) the effect can be abolished or reversed by the intravenous injection of ergotamine tartrate (1 mg. per kg.); (b) there is some indication, perhaps, that the response can be intensified by the intravenous injection of a weak cocaine-hydrochloride solution and; (c) a saline extract of the subcutaneous tissue reveals on intravenous injection appreciable quantities of epinephrine as long as previous massage of this area was followed by a pronounced pressor effect.

It is a surprising fact that a typical and pronounced pressor effect as a result of massage could be elicited as late as 19 hours after the subcutaneous injection of 1 cc. of epinephrine and that a saline solution extract of this subcutaneous tissue possessed marked pressor effect on intravenous injection.

The importance of these findings and their application in the therapeutic use and diagnostic value of epinephrine (Goetsch test) are more or less obvious but will be discussed in the detailed report.