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4. Læwen A: Experimentelle Untersuchungen über die Möglichkeit den Tetanus mit Curarin zu behandeln. Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie 16:802, 1906

Anesthesiology
73:190, 1990

In Reply:—The previous letter by one of us was not concerned with the history of curare in anesthesia, but rather with early observations on the critically important effect of curare on the upper airway.¹ Nonetheless, the letter did make reference to the introduction of curare into anesthetic practice, and Dr. Goerig's communication raises some interesting questions on that point.

It is clear that H. R. Griffith and G. E. Johnson of Montreal, Canada were not the first to administer curare to anesthetized patients. A group of American anesthesiologists are said to have assessed the muscle-relaxing properties of a semi-refined preparation of d-tubocurarine in at least two patients in the 1930s, but to have discontinued its use because of concern about total respiratory paralysis.² As outlined in Dr. Goerig's letter, a German surgical registrar named Laewen gave a preparation of calabash curare called "Curarin" to a number of surgical patients in about 1912.³ His purpose was to see if it would produce abdominal wall relaxation during light anesthesia. Laewen observed this effect but did not continue to use or study Curarin, apparently because of a limitation of reliably potent supplies.

Both of these early experiences with curare in the context of anesthesia are of historic interest. However, as far as can be ascertained, neither led to its use by other anesthetists or surgeons of the time, and hence neither can be considered to have launched curare into anesthetic practice. Its use in anesthesia occurred only after publication of the well-known clinical study of Griffith and Johnson in 1942, which showed that a relatively pure and stable preparation of curare could produce "excellent muscular relaxation" reliably and safely in anesthetized patients.⁴

Although Laewen cannot be credited for having introduced curare into the practice of anesthesia, he is certainly worthy of recognition in the history of anesthesia. He appears to have been the first to have correctly perceived how a neuromuscular blocking agent can be employed to advantage during anesthesia; the first to have studied curare in animal models for this particular purpose (in mice and guinea pigs); and the first to have administered curare and observed its principal beneficial effect in anesthetized humans. Even though the dose of the curare preparation he administered by the subcutaneous or intramuscular route seems to have been quite small,⁵ he found that "the effect during suturing of the abdominal wall was obvious and desirable."³ His 1912 article is fascinating, not only with respect to the suggested

5. Karg: Die Behandlung des Tetanus mit Curare. Langenbecks Archiv 29:338, 1883
6. Griffith HR, Johnson GE: The use of curare in general anesthesia. ANESTHESIOLOGY 3:418, 1942

(Accepted for publication April 10, 1990.)

usefulness of curare during anesthesia, but also with respect to another novel idea for that time—the use of regional analgesia after abdominal surgery to improve ventilatory function and thereby prevent postoperative atelectasis and pneumonia! Laewen seems to have been a highly inquisitive and innovative surgical registrar who saw solutions to important anesthetic problems many years before they were thought of again and introduced into practice. He was decades ahead of his time.

We concur completely with a message implicit in Dr. Goerig's letter, *i.e.* that older literature can be most interesting, even instructive—yet easily overlooked. Indeed, that was the theme of the previous communication from one of us concerning curare and the upper airway.¹

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(Accepted for publication April 10, 1990.)

Anesthesiology
73:190–191, 1990

Preparation of Oral Naltrexone Solution

To the Editor:—Since publication of our paper¹ regarding the use of prophylactic naltrexone to prevent pruritus associated with epidural morphine, I have received several phone calls from pharmacists and anesthesiologists inquiring about the method of preparation of naltrexone as an oral solution. Naltrexone is available in 50-mg tablets, and the dose we recommend for prevention of pruritus is 5–6 mg. The 50-mg tablet is crushed and dissolved in 50 ml of water, and we

administer 5–6 ml of the solution (5–6 mg) plus 4 ml of any flavored syrup orally within 5 min of administration of morphine. The solution is stable for 24 h.

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Anesthesiology
73:191, 1990

Aortic-to-Radial Arterial Pressure Gradient after Bypass

To the Editor:—The interesting paper by Pauca *et al.*¹ correctly identifies the source of the aortic-to-radial pressure gradient following cardiopulmonary bypass as a decrease in “hand vascular resistance.” I would like to propose an hypothesis for this as yet incompletely understood decrease.

Most centers subject cardiac surgical patients to hemodilution during bypass to a hematocrit around 20%. This decreased hematocrit reduces blood viscosity to approximately one half of normal.^{2,3} Such viscosity reduction should decrease arteriolar resistance to approximately one half of normal, since resistance is a linear function of viscosity, according to the Poiseuille equation. A decrease in systemic vascular resistance following bypass has indeed been reported in patients with a normal ventricle during coronary surgery³; this was compensated for by increased cardiac output.^{2,3} This reduction of resistance takes place without vasodilatation, as was shown long ago by Gordon *et al.*⁴ Due to the peculiar physical characteristics of blood, such reduction could be even more marked at the microcirculatory level.⁵

The difference between “peripheral” and “systemic” vascular resistance in the arteries normally is negligible, since the peripheral arteriolar resistance is much larger than the proximal arterial resistance. However, from the physical point of view, a long tube such as the brachial and radial artery does necessarily present a resistance, however small, to blood flow. Thus, systemic vascular resistance should be understood as the sum of two resistances in series (fig. 1), one proximal and one distal. Systemic vascular resistance takes into account both the proximal and distal components and determines the mean aortic pres-

sure; peripheral vascular resistance, equal to the distal component, considers only arterioles and capillaries and determines the mean distal arterial pressure (fig. 1). If the distal resistance decreases markedly and the proximal component increases, as seems to be the case in these patients, a gradient appears between aortic and distal pressures.

Reduced peripheral vascular resistance downstream from the radial cannula tends to decrease the pressure drop across arterioles and capillaries, as the pressure difference is a direct function of resistance. A decreased radial arterial pressure ensues. Inasmuch as the arteries are elastic tubes, a reduction in transmural pressure should result in a decrease of the arterial diameter. According to Poiseuille, a smaller arterial diameter would increase the proximal resistance. Therefore, the normally very small decrease in mean pressure between aorta and radial artery becomes more marked. Thus, purely passive hydraulic factors secondary to hemodilution would explain the decrease in peripheral resistance and the increase in “proximal” arterial resistance underlying the aortic-to-radial pressure drop.

It has been suggested that the difference between aortic and radial pressures would invalidate all previous work describing hemodynamics immediately after cardiopulmonary bypass, since this work relied on radial artery rather than aortic pressure measurement. This objection may be justified if, in order to calculate afterload or ventricular work, aortic pressure was extrapolated from radial artery measurements. However, for estimation of peripheral resistance and of perfusion pressure, the correct value is not the aortic but the distal arterial pressure, as this is the pressure that most tissues (except, of course, the heart) effectively “see.”

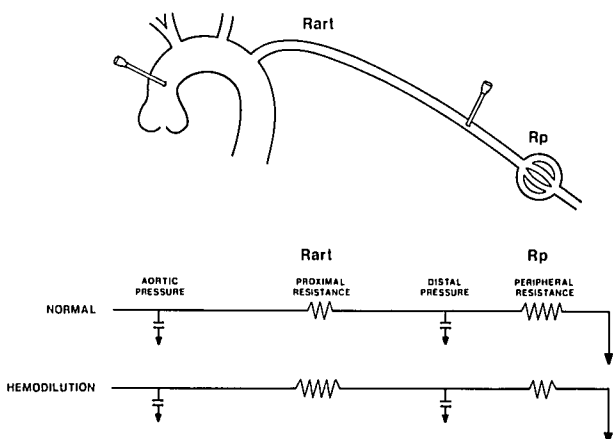


FIG. 1. Total arterial resistance to flow results from the sum of a proximal resistance (R_{art}), related to the size of the tube, and a peripheral resistance (R_p), determined by arterioles, capillaries, and blood viscosity. Normally R_{art} is negligible compared to R_p ; however, in the presence of hemodilution, R_p and the distal pressure decrease. Since the arterial diameter is consequently reduced, R_{art} increases and a pressure gradient originates between the aortic and the distal pressures.

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(Accepted for publication April 10, 1990.)

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(Accepted for publication April 11, 1990.)