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The History of the Bezold-Jarisch Effect

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With 3 Figures in the Text

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1. Early experiments with veratrum alkaloids

In 1862, in the course of his studies on the innervation of the heart VON BEZOLD[6] came to the conclusion that there were sensory vagal fibers originating in the heart whose stimulation had a vasodepressor effect. This antedated by three years the discovery of the depressor nerves of the aorta by LUDWIG and VON CYON[41]. In 1867, VON BEZOLD and HIRT[7] observed that medium doses of veratrine caused a decrease in blood pressure, which could be prevented by sectioning the vagus nerves, and which could not be fully explained by the accompanying bradycardia. VON BEZOLD explained the vasodepressor action as due to a stimulation by veratrine of the sensory nerve endings of the vagus he had recognized earlier, and of the depressor nerves. He assumed the nerve endings to be spread out under the inner surface of the heart, and their stimulation to lead to reflex inhibition of the vasomotor center thus causing vasodilatation. VON BEZOLD and HIRT did not clearly decide on the relative importance of the vagal fibers versus the true depressor fibers; nor did v. BEZOLD advance conclusive proof that sensory vagal fibers from the lungs or from the abdominal area were not

* During the XIX International Physiological Congress in Montreal, Canada, August 31 to September 4, 1953, a symposium was held on September 2 entitled: Reflexes from the cardiac and pulmonary areas. (SCHMIDT, Philadelphia, chairman; HEYMANS, Ghent; KRAYER, Boston; DAWES, Oxford; ZOTTERMAN, Stockholm; WHITTERIDGE, Edinburgh). Professor JARISCH had accepted an invitation to participate but was unable to attend because of illness. When I was asked to take the place of Professor JARISCH, I decided to present "The history of the BEZOLD-JARISCH effect". Because the invitation was extended to me close to the starting date of the Congress, the manuscript was not ready for printing in the Abstracts of Communications of the XIX International Physiological Congress. Hence this contribution to the symposium remained unpublished. I am grateful to the editors of Naunyn Schmiedeberg's Archiv für experimentelle Pathologie und Pharmakologie that they have considered publishing this article as a fitting tribute to Professor JARISCH on the occasion of his 70th birthday.

responsible for the vasodepressor effect. However, he thought of and rejected both possibilities.

Of the investigators of the pharmacology of the veratrum alkaloids before 1920, LISSAUER in 1887, using cevadine, rejected VON BEZOLDS interpretation of the mechanism of the vasodepressor action[40]. WATTS EDEN in 1892[47], on the other hand, considered it possible to ascribe the vasodepressor effect of small doses of protoveratrine to the reflex inhibition of the vasomotor center caused by stimulation of the depressor nerves. In 1915 CRAMER[10], working with an alkaloidal extract from Veratrum viride, confirmed VON BEZOLDS concept of a reflex decrease in blood pressure due to vasodilatation. As a rule, this effect was accompanied by a reflex decrease in heart rate and by a reflex slowing or stoppage of the respiration. All these effects could be reliably seen only if small doses were used. They were dependent upon the integrity of the vagus. However, CRAMER, probably under the influence of the studies of BRODIE and RUSSELL[9], ascribed the effect to a selective action of the Veratrum viride alkaloids on the afferent nerve endings of the vagus in the lungs. In his review on veratrine and protoveratrine in 1920 BOEHM[8], in whose laboratory LISSAUER and WATTS EDEN had done their work, did not resolve the controversy between the authors referred to. BOEHM, however, concisely stated VON BEZOLDS concept: "The primary fall in blood pressure is explained by VON BEZOLD and HIRT by the stimulation of (sensory) depressor cardiac nerves which are carried in the stem of the vagus nerves and whose effectiveness according to VON BEZOLD may surpass that of the true depressor nerves."

2. The circulatory action of Viscum album

In 1935 JARISCH and HENZE began experimental studies on the circulatory action of Viscum album L., the European mistletoe. Blood pressure fall and heart rate decrease caused by extracts of the active principles could be abolished or prevented by cutting the vagi or by cold block. HENZE and JARISCH found the Viscum album principles still fully active under the conditions 1, 2 and 3 illustrated in Fig. 1: after denervation of the aorta and the origin of the big vessels (by severing their sheaths, thus dividing the depressor nerves and the sympathetic outflow to the heart) at 1; after the vagus had been cut below the heart, at 2; after the lungs had been denervated, at 3. On the other hand, after sectioning of the cardiac vagal fibers — at 4 — only a slight blood pressure decrease occurred. Finally, after severing all nervous connections of the heart — at 1 and at 4 — the Viscum album extract became inactive, indicating that the effect to some extent could be elicited via the depressor nerves.

The result of this work published in 1937 and in a series of subsequent publications*, gave evidence of a vasodepressor and cardiodecelerator reflex originating in the heart, and carried by afferent vagal fibers; a reflex, similar in general to the depressor reflex and the carotid sinus reflex but independent of both. Corroborative evidence for the reflex nature of the phenomenon was advanced showing that a reciprocal inhibition of accelerans activity accompanied the reflex bradycardia, and an increase in organ volume — especially of the liver — accompanied the reflex decrease in blood pressure[19,43,44].

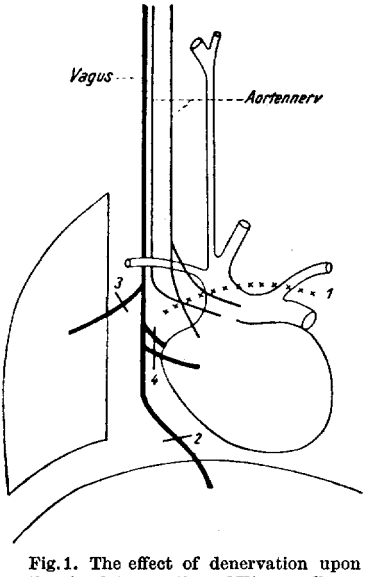

Fig. 1. The effect of denervation upon the circulatory action of *Viscum album*. For explanation see text. (Reprinted from A. JARISCH: Wien. klin. Wschr. **1938**, 1032)

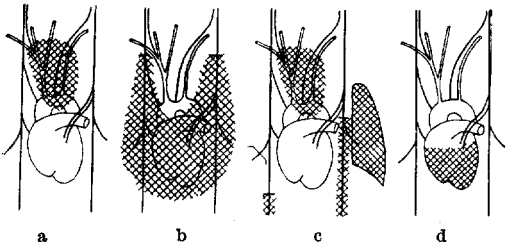

Fig. 2 a—d. The effect of denervation upon the circulatory action of veratrine. For explanation see text. [Reprinted from A. JARISCH: Arch. Kreisl.-Forsch. **7**, 260 (1940)]

3. Experiments with veratrine. The Bezold effect

Searching for other substances with similar action, JARISCH and his associates became aware of veratrine through the review of BOEHM[8] who referred to VON BEZOLD and HIRTS observation, as mentioned above.

Thereupon extensive systematic studies, also concerning the anatomy and physiology of the cardiac nerves, were initiated to substantiate VON BEZOLDS concept**. In 1939 JARISCH and RICHTER published their work on veratrine (in the cat), in which they utilized the techniques employed in the study of Viscum album. Their results concerning the vasodepressor and cardiodecelerator action of veratrine JARISCH has diagramatically represented in Fig. 2, regarding the influence of denervation. They were as follows:

a) Denervation of aorta and origin of large vessels had no influence.

b) If the innervation of aorta and large vessels was left intact, but the heart and lungs were denervated, then the effect had disappeared.

* 14,18,20,21,30. — ** 2,22,23,31–34,45.

c) If the aorta and the origin of the large vessels were denervated, the left lung was denervated and the main bronchi were taken out of their sheaths, the right lung was removed, and the vagi were cut above diaphragm, then no influence upon the veratrine effect was noticeable.

d) If the innervation of aorta, lungs and atria of the heart was left intact, but the ventricular nerves were blocked by epicardial anesthesia, then the veratrine effect was absent or was much reduced.

JARISCH and RICHTER concluded that VON BEZOLDs interpretation of the (primary) blood pressure decreasing action of veratrine was correct.

Impressed by the bold concept of VON BEZOLD, who — as JARISCH once put it — had anticipated by 70 years the modern concept of chemosensitivity of the regulatory nerves, JARISCH, in 1939, designated as BEZOLD effect the cardiovascular and cardiocardiac reflex revealed by veratrine and by the active principles of Viscum album[33].

According to JARISCHs definition the apparatus of the BEZOLD effect consists of: a) the reflexogenous zone in the heart predominantly in the ventricular muscles; b) the afferent pathways in the vagi; c) the efferent pathways, composed—as with all depressor reflexes—of two divisions, one in the vasomotor pathways to the vessels, the other returning to the heart via the vagus.

4. The detector substances

Veratrine and the active principle of Viscum album were the first of a large series of substances which JARISCH named "detector substances" of the BEZOLD effect. Between 1941 and 1943 aconitine[17], histamine[29], potassium ion[1], adenosine and ATP[24], among others[27], were found by JARISCH and his associates to exert effects which put them into this classification. Antagonists to the detector substances also were uncovered such as calcium ion[1,29], local anesthetic agents, and antihistaminic agents [15,16]. Other investigators have added to this list. There is doubt in my mind whether or not many of the substances deserve their classification as detector substances of the BEZOLD effect. A discussion of the controversial issue is not profitable at present; nor do I consider myself competent to undertake it.

However, a few points of general importance concerning the use of so-called detector substances deserve to be mentioned. Since the strongest experimental support for the existence of the BEZOLD effect resulted from work with veratrum alkaloids, my comments will be restricted to these substances. Only the ester alkaloids of the tertiary amines are active. All these ester alkaloids exert effects on various excitable structures and—depending upon the dose, or upon experimental procedures of localizing the agent—the overall effect may be more or less complex[36,37].

It is well known that the veratrum ester alkaloids cause vasodepressor and cardiodecelerator action from various areas outside the

heart. Such effects JARISCH and his associates have themselves been able to elicit from the lungs[2] and from the carotid body[31]. Others have shown that, apart from these sites, areas closer to the central nervous system, or within it, also may respond in the same way. If the doses of the active alkaloids are large, the chances are especially great that more than one of these areas will participate in the overall circulatory response; in addition, large doses may cause effects qualitatively different from those of small doses. CRAMER, as mentioned above, emphasized the necessity of using small doses in order to clearly demonstrate the reflex circulatory (and respiratory) action of veratrum viride.

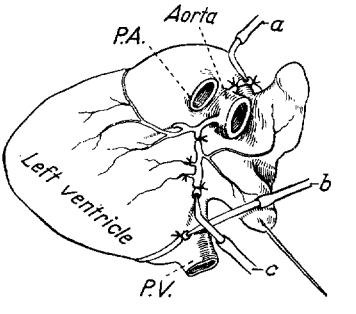

Fig. 3. Left lateral diagram of preparation for simultaneous perfusion of the coronary arteries of the dog. Cannulae are shown in the right coronary artery (*a*); the peripheral end of the left circumflex (*b*); and the central end of the left circumflex (*c*) which now feeds only the left superior atrial coronary artery. The aorta, pulmonary artery (*P.A.*) and pulmonary veins (*P.V.*) have been divided. [Reprinted from G. S. DAWES: J. Pharmacol. exp. Ther. 89, 325 (1947)]

Even small doses, in the intact animal, can readily find access to several sensitive targets. For this reason, the studies conducted in my own laboratory with veratrum ester alkaloids attempted the localization of the agent to a particular site by using suitable preparations such as the innervated heart-lung preparation or other perfusion techniques[38,39,42].

It is the great merit of DAWES[12,13] to have combined the use of smallest effective doses with their localized administration to the decisive target by injecting the veratrum ester alkaloids into the coronary arteries or into segments thereof, as illustrated in Fig. 3. This, in 1947, has provided positive proof that it is indeed possible to elicit a reflex depressor and reflex cardiodecelerator effect (dependent upon the integrity of the vagus) from the heart itself; that is, in the cat from the area supplied by the right and left coronary arteries, and in the dog exclusively from the area supplied by the circumflex branch of the left coronary artery, or mainly from the left ventricle. The observations of DAWES were confirmed in the laboratory of SCHMIDT[4,5]. In some of these experiments the skillful use of catheterization techniques allowed localized administration to the coronary circulation while at the same time obviating the severe surgical procedures required in DAWES' experiments.

5. Electrophysiological studies

Ten years ago, in 1943, JARISCH began to interest the physiologists in the electrophysiological investigation of the afferent "BEZOLD path-

way". A large body of work initiated by AMANN and SCHAEFER[3] was recently reviewed by SCHAEFER[46]. Subsequent important studies were conducted by JARISCH and ZOTTERMAN[35]. You will hear more about the fibers involved in the BEZOLD effect from the other speakers of this symposium, DAWES[11], ZOTTERMAN[49] and WHITTERIDGE[48].

6. The meaning of the Bezold effect

JARISCH himself[26,28] has advanced many stimulating and challenging arguments in favor of considering the BEZOLD effect as an endophylactic trophotropic protective reflex in the sense of HESS, coming into action, for example, in fainting. Others, although no longer denying the existence of the BEZOLD effect, are of the opinion that neither the structure of the receptors, nor the adequate stimulus, nor the meaning is known as yet*.

7. Bezold-Jarisch effect versus Bezold effect

The term BEZOLD effect, introduced by JARISCH in 1939, has been used for the circulatory reflex discussed above. Considering the evidence presented, it is obvious that the substantiation of the concept rests largely upon an independent discovery of JARISCH followed by a vast amount of searching and skillful experimental work, which JARISCH himself conducted together with his coworkers; or which JARISCH inspired, or provoked, others to carry out. As early as 1942 STRUGHOLD and BENZINGER[25] added JARISCH's name to that of von BEZOLD when speaking about the BEZOLD effect; I share their opinion that ADOLF JARISCH's work should be generally recognized by designating as BEZOLD-JARISCH Effect the cardiogenous reflex which he established.

References

[1] AMANN, A., and A. JARISCH: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **201**, 46 (1943).

[2] AMANN, A., and H. RICHTER: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **196**, 274 (1940).

[3] AMANN, A., and H. SCHAEFER: Pflügers Arch. ges. Physiol. **246**, 757 (1943).

[4] AVIADO, D. M., jr., R. G. PONTIUS and C. F. SCHMIDT: J. Pharmacol. exp. Ther. **97**, 420 (1949).

[5] AVIADO, D. M., jr., T. H. LI, W. KALOW, C. F. SCHMIDT, G. L. TURNBULL, G. W. PESKIN, M. E. HESS and A. J. WEISS: Amer. J. Physiol. **165**, 261 (1951).

[6] BEZOLD, A. VON: Untersuchungen über die Innervation des Herzens, 1862 (quoted from reference 7).

[7] BEZOLD, A. VON, u. L. HIRT: Untersuchungen aus dem physiol. Lab. Würzburg. 1867, S. 73.

[8] BOEHM, R.: Heffter's Handbuch der exper. Pharmakologie 2. Part 1, 249 (1920).

* For recent references to the BEZOLD-JARISCH effect and its role see Physiol. Rev. **40**, Suppl No. 4, 1960: E. NEIL, 201—208; H. SCHAEFER, 213—231; and Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. 25. Tagung. Darmstadt: Steinkopff 1959. K. KRAMER, 142—163.

[9] Brodie, T. G., and A. E. Russell: J. Physiol. (Lond.) **26**, 92 (1900).
[10] Cramer, W.: J. Pharmacol. exp. Ther. **7**, 63 (1915).
[11] Dawes, G. S.: Abstr. of Comm., XIX Internat. Physiol. Congress, Montreal, 1953, p. 51.
[12] Dawes, G. S.: J. Pharmacol. exp. Ther. **89**, 325 (1947).
[13] Dawes, G. S., J. C. Mott and J. G. Widdicombe: Brit. J. Pharmacol. **6**, 675 (1951).
[14] Ebster, H., and A. Jarisch: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **145**, 298 (1929).
[15] Eichholtz, F., A. Fleckenstein and R. Muschaweck: Klin. Wschr. **1949**, 71.
[16] Fleckenstein, A., R. Muschaweck and F. Bohlinger: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **211**, 132 (1950).
[17] Geilenkirchen, H.: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **198**, 274 (1940).
[18] Henze, C.: Arch. int. Pharmacodyn. **53**, 44 (1936).
[19] Henze, C., and A. Jarisch: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **191**, 30 (1938).
[20] Henze, C., and K. F. W. Ludwig: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **187**, 694 (1937).
[21] Jarisch, A.: Wien. klin. Wschr. **1938**, 1032.
[22] Jarisch, A.: Arch. Kreisl.-Forsch. **7**, 260 (1940).
[23] Jarisch, A.: Arch. Kreisl.-Forsch. **9**, 1 (1941).
[24] Jarisch, A.: Klin. Wschr. **1941**, 1045.
[25] Jarisch, A.: Vom Herzen ausgehende sensible Erregungen. Schriften der deutschen Akademie der Luftfahrtforschung. **7**, 61 (1943) (see discussion).
[26] Jarisch, A.: Die Ohnmacht und verwandte Zustände als biologisches Problem. Klin. Med. **3**, 956 (1948).
[27] Jarisch, A.: Wien. klin. Wschr. **1949**, 551.
[28] Jarisch, A.: Z. phys. Ther. **3**, 7 (1950).
[29] Jarisch, A., A. Amann and H. Richter: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **198**, 158 (1941).
[30] Jarisch, A., and C. Henze: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **187**, 706 (1937).
[31] Jarisch, A., and H. Richter: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **193**, 347 (1939).
[32] Jarisch, A., and H. Richter: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **193**, 355 (1939).
[33] Jarisch, A., and H. Richter: Klin. Wschr. **1939**, 185.
[34] Jarisch, A., H. Richter and H. Thoma: Klin. Wschr. **1939**, 1440.
[35] Jarisch, A., and Y. Zotterman: Acta physiol. Scand. **16**, 31 (1948).
[36] Krayer, O.: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **209**, 405 (1950).
[37] Krayer, O., and G. H. Acheson: Physiol. Rev. **26**, 383 (1946).
[38] Krayer, O., G. K. Moe and R. Mendez: J. Pharmacol. exp. Ther. **82**, 167 (1944).
[39] Krayer, O., E. H. Wood and G. Montes: J. Pharmacol. exp. Ther. **79**, 215 (1943).
[40] Lissauer, H.: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **23**, 36 (1887).
[41] Ludwig, Carl, and E. von Cyon: Arbeiten aus dem physiol. Institut Leipzig **18**, 307 (1866).
[42] Moe, G. K., D. L. Bassett and O. Krayer: J. Pharmacol. exp. Ther. **80**, 272 (1944).
[43] Richter, H.: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **191**, 40 (1938).

[44] RICHTER, H., and H. SCHRÖCKSNADEL: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **191**, 23 (1938).
[45] RICHTER, H., and H. THOMA: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **193**, 355 (1939).
[46] SCHAEFER, H.: Ergebn. Physiol. **46**, 71 (1950).
[47] WATTS EDEN, T.: Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **29**, 440 (1892).
[48] WHITTERIDGE, D.: Abstr. of Comm., XIX Internat. Physiol. Congress, Montreal 1953, p. 66.
[49] ZOTTERMAN, Y.: Abstr. of Comm., XIX Internat. Physiol. Congress, Montreal. 1953, p. 59.

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