SCIENCE

VOL. 78 FRIDAY, JULY 21, 1933 No. 2012

SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. MCKEEN CATTELL and published every Friday by

THE SCIENCE PRESS

New York City: Grand Central Terminal
Lancaster, Pa. Garrison, N. Y.
Annual Subscription, $6.00 Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the Association may be secured from the office of the permanent secretary, in the Smithsonian Institution Building, Washington, D. C.

CHEMICAL MEDIATORS OF AUTONOMIC NERVE IMPULSES[1]

By Professor WALTER B. CANNON

LABORATORIES OF PHYSIOLOGY, HARVARD MEDICAL SCHOOL

THE foremost physiologists of the world have given years of their professional activity to research on the contraction of skeletal muscle. Its more humble cousin, smooth muscle, which thrusts us into the world, and which for decades supports by its services our nutritive functions and our conscious existence, has had relatively little attention. The slow action of smooth muscle, its peculiar innervation, its special responsiveness to humoral agents and to certain drugs render it an especially convenient and promising agency for physiological analysis. And the results obtained by such analysis may have significant bearings on processes elsewhere in the organism—on the nature of stimulation and inhibition, for example, and on the effects of biochemical and pharmacological agents.

[1] Read at the joint meeting of the Federation of American Societies of Experimental Biology at Cincinnati, Wednesday, April 12, 1933.

The autonomic system characteristically innervates smooth muscles and glands. In this paper I propose to direct attention only to smooth and cardiac muscle, and I hope to bring before you observations which have importance for physiologists, biochemists and pharmacologists.

As preliminary to a consideration of the chemical mediators of autonomic nerve impulses it is well to learn what is known regarding autonomic nerve endings. During the past 60 years some histologists have represented nerve filaments as actually penetrating smooth muscle cells; their testimony, however, has not been accepted because of untrustworthy technique and also because other competent histologists described endings on the cell surface. To Boeke[2] is credited the first reliable evidence that the nerve twig enters the muscle fiber and ends there in a fine

[2] J. Boeke, *Verhandel. d. Koninkl. Akad. v. Wetensch.*, Amsterdam, xxiii: 1416, 1915.

reticulum, often close to the nucleus. Boeke's studies were made on the ciliary muscle of the human eye. His observations were confirmed by Stöhr[3] in a study of the neuromuscular elements of the human urinary bladder, by Lawrentjew[4] and by Hill[5] in the intracytoplasmic nerve endings in the contractile cells of the bladder, stomach and intestine. Lawrentjew has figured instances of depression in the nucleus in which the terminal nerve net is present and other instances of partial or complete encircling of the nuclear body by the nerve filament. The fact appears to be well established that nerve impulses are not merely brought to the surface of smooth-muscle cells, but are delivered to the interior, in the region of the nucleus.[6]

Another point of considerable interest is the failure of histologists to find two distinct neurone endings in the same muscular element. Since there are areas of smooth muscle, such as those of the intestinal wall, which are under more or less antagonistic sympathetic and parasympathetic control, we might expect to find representatives of these two divisions of the autonomic system present, at least occasionally, in single cells. I have not been able to discover, however, any evidence in support of that arrangement. The alternative mode of organization would be the supply of sympathetic fibers to some muscle cells and of parasympathetic fibers to others.

A third significant fact reported by histologists is their inability to find nerve filaments distributed to all smooth-muscle cells. Since 1850 nearly a dozen investigators have reported that not every cell receives a nerve ending. This negative testimony might be attributed to defects of technique. Recently, however, Stöhr[7] has reported that he has examined large numbers of preparations most carefully and, finding a lower ratio than one cell in a hundred with a nerve supply, he has declared that he will not believe in the dependence of each muscular unit on direct nervous control until there is clear proof to the contrary. In the ciliary muscle of the eye, however, Boeke[6] described, last year, the presence of so rich a display of nerve terminals in the contractile mass that he infers the possibility that every fiber received a nerve ending. He suggests that the meagerness of innervation, previously found in other smooth-muscle structures, is explicable in the difficulties of staining. At present, therefore, the question must remain open.

If there is not a detailed one-to-one relation between nerve ending and smooth-muscle cell the impulse delivered to the special innervated cell might be effective on neighboring common cells by either a physical or a chemical agency of transmission. The view that smooth muscle is a syncytium, with the elements united by protoplasmic bridges, has been both affirmed and denied.[8,9] Whether bridges are present or not, we now have evidence that a chemical agency set free by nervous influence in muscle cells in one region can affect other, remotely situated muscle cells which have been completely deprived of their autonomic innervation. The requirement of an individual nerve supply for each contractile fiber is thereby rendered unnecessary.

That autonomic nerve impulses liberate chemical substances in muscle was first shown by Loewi[9a] in 1921. As is well known, he then reported that Ringer solution resting in contact with a frog heart which has been checked by vagal stimulation is given a new property, that of being able to induce in another heart the typical vagal effects. And when the cardio-accelerator nerves are stimulated the solution is endowed with typical sympathomimetic properties. Although these observations have failed to be confirmed by such competent investigators as Asher[10] and E. and P. Gley,[11] others, notably Plattner,[12] Kahn,[13] Samoiloff[14] and Bain,[15] have brought confirmation of Loewi's experiments (for reviews see H. Frédéricq,[16] and Demoor[17]). By perfusing with dilute defibrinated blood the cat or rabbit heart, while stimulating its nerves, Rylant[18] was able to reproduce in warm-blooded animals the effects obtained by Loewi and others on the frog and tortoise. The evidence supporting Loewi's testimony seems now to be conclusively favorable.

Substances mimicking the action of vagal nerve impulses are not only given off from the heart but also from other structures. For example, Engelhart[18a] has

[3] Ph. Stöhr, Jr., *Zeitschr. f. Anat. u. Entwicklungsgesch.*, lxxviii: 555, 1926.

[4] B. J. Lawrentjew, *Zeitschr. f. mik.-anat. Forsch.*, vi: 467, 1926.

[5] C. A. Hill, *Phil. Trans. Roy. Soc.*, London, B ccxv: 355, 1927.

[6] Cf. J. Boeke, *Jour. Comp. Neurol.*, lvi: 27, 1932.

[7] Ph. Stöhr, Jr., "Mik. Anat. d. Veg. Nerv. Syst.," Berlin, p. 107, 1928.

[8] C. McGill, *Am. Jour. Anat.*, ix: 493, 1909.

[9] O. W. Tiegs, *Austr. Jour. Exp. Biol. and Med. Sci.*, i: 131, 1924.

[9a] O. Loewi, *Arch. f. d. ges. Physiol.*, clxxxix: 239, 1921. Also cxciii, 201, 1922.

[10] L. Asher, *Arch. f. d. ges. Physiol.*, cxciii: 84, 1922. Also *ibid.*, 1925, ccx, 689. *Zeitschr. f. Biol.*, lxxviii: 297, 1923.

[11] E. Gley and P. Gley, *C. r. Soc. de Biol.*, xciv: 269, 1926.

[12] F. Plattner, *Zeitschr. f. Biol.*, lxxxiii: 544, 1925.

[13] R. H. Kahn, *Arch. f. d. ges. Physiol.*, ccxiv: 482, 1926.

[14] A. Samoiloff, *Arch. f. d. ges. Physiol.*, ccxvii: 582, 1927.

[15] W. A. Bain, *Quart. Jour. Exper. Physiol.*, xxii: 269, 1932.

[16] H. Frédéricq, *C. r. Soc. de Biol.*, xcvii: Réunion plénière, May 27–28, 1927.

[17] J. Demoor, *Ann. de Physiol. et de Phys.-Chem. Biol.*, v: 58, 1929.

[18] P. Rylant, *C. r. Soc. de Biol.*, xcvi: 1054, 1927.

[18a] E. Engelhart, *Arch. f. d. ges. Physiol.*, ccxxvii: 220, 1931.

found that after the smooth muscle of the ciliary body and the iris has been contracted by oculomotor stimulation, the aqueous humor exhibits a new, markedly inhibitory action on the tortoise heart. Furthermore, Bain (1932) has reported that fluid flowing through vessels of the tongue, while the smooth muscle of the walls was being relaxed by stimulation of the lingual nerve, acquires properties which make it excitatory to the muscle of the rabbit intestine. And finally Gibbs and Szelöczey[19] have demonstrated, by perfusing the cat submaxillary gland during periods of electrical excitation of the chorda tympani, that the Ringer solution which has passed through the vessels can cause fall of blood pressure, excitation of salivary flow, inhibition of the isolated frog heart and augmented activity of the isolated intestine. All these experiments, consistent in showing that a parasympathomimetic substance is given off when various cranial autonomic nerves are excited, indicate that the term "vagus substance," proposed by Loewi, is not sufficiently broad. "Parasympathin" would be a more inclusive term, shorter than "parasympathicusstoff" suggested by Engelhart (1931).

In 1929 Demoor cast doubt on the idea that in natural conditions autonomic nerve impulses cause liberation of substances mimetic of nerve impulses. The artificial irrigation of the heart, he declared, might create new conditions for the tissues, accompanied by an unphysiological permeability of cell membranes and a consequent abnormal escape of chemical agents having vagal or sympathetic effects. So far as the so-called "chorda substance" is concerned, Demoor's skepticism has been effectively countered by the experiments of Babkin, Gibbs and Wolff,[20] unless objection can be raised to their use of physostigmine. They have been able to obtain a clear fall of blood pressure, and also a secretion of saliva from the opposite denervated submaxillary gland (*cf.* Babkin, Alley and Stravraky[21]) on stimulating the chorda tympani, while the blood was normally circulating.

There is good evidence, likewise, that the sympathetic substance is released from excited cells under physiological conditions. To be sure, the experiments of Brinkman and Van Dam,[22] Lanz[23] and Külz,[24] showing that a substance from the nervously accelerated heart has a sympathomimetic inhibitory action on gastric peristalsis, and also the experiment of Finkelman demonstrating a chemical transfer of inhibitory action from a nervously inhibited piece of gut to another, denervated piece, were performed with salt solution as a vehicle. In these instances, therefore, Demoor's criticism might be pertinent. The experiments of Newton, Zwemer and Cannon,[25] of Cannon and Bacq[26] and of Rosenblueth and Cannon[27] have proved, however, that the heart, the salivary gland and the nictitating membrane, deprived of sympathetic innervation, exhibit responses characteristic of sympathetic influence when smooth muscle of remote regions is stimulated by way of sympathetic nerves, and when the only communication is through the blood stream. The evidence seems quite clear that not only are sympathomimetic and parasympathomimetic substances produced when smooth or cardiac muscle is stimulated by corresponding nerves, but that these substances diffuse out from the affected organs into the circulating blood and under appropriate conditions can have typical mimetic effects on distant organs.

What is the nature of these substances? Examination of the vagus substance has shown that it is dialyzable, that it is stable in an acid but not in an alkaline medium, and that it is rapidly destroyed by a blood or tissue esterase.[28,29] In general it appears to be a highly labile and very active ester of choline and possibly acetylcholine itself. The vagus substance and acetylcholine both act the same on the frog heart, both are very sensitive to substances in minced organs and in blood, the destruction of both by cellular extracts is checked by physostigmine, and if the vagus substance has been rendered inactive by such extracts it can be restored by acetylization.[30]

The chorda substance likewise resembles acetylcholine. The two have the same effects on blood pressure, salivary secretion, cardiac rate and intestinal rhythm. Both are destroyed by blood, and this destruction can be prevented by physostigmine. In one respect, in the experience of Gibbs and Szelöczey (1932), do the two differ—the chorda substance when biologically assayed is sometimes not so quickly destroyed in blood as is acetylcholine. They state that otherwise they have not been able to find any difference between the two substances.

Until a few months ago the evidence was fairly con-

[19] O. S. Gibbs and J. Szelöczey, *Arch. f. exper. Pathol. u. Pharmakol.*, clxviii: 64, 1932.

[20] B. P. Babkin, O. S. Gibbs and H. G. Wolff, *Arch. f. exper. Pathol. u. Pharmakol.*, clxviii: 32, 1932.

[21] B. P. Babkin, A. Alley and G. W. Stravraky, *Trans. Roy. Soc. Canada*, Sec. v, 89, 1932.

[22] R. Brinkman and E. Van Dam, *Arch. f. d. ges. Physiol.*, cxcvi: 66, 1922.

[23] A. B. Lanz, *Arch. néerl. de Physiol.*, xiii: 423, 1928.

[24] F. Külz, *Arch. f. exper. Pathol. u. Pharmakol.*, cxxxiv: 252, 1928.

[25] H. F. Newton, R. L. Zwemer and W. B. Cannon, *Am. Jour. Physiol.*, xcvi: 377, 1931.

[26] W. B. Cannon and Z. M. Bacq, *ibid.*, xcvi: 392, 1931.

[27] A. Rosenblueth and W. B. Cannon, *ibid.*, xcix: 398, 1932.

[28] W. R. Witanowsky, *Arch. f. d. ges. Physiol.*, ccviii: 694, 1925.

[29] O. Loewi and E. Navratil, *ibid.*, ccxiv: 678, 689, 1926.

[30] E. Engelhart and O. Loewi, *Arch. f. exper. Pathol. u. Pharmakol.*, cl: 1, 1930.

sistent that the substance set free from the heart on sympathetic stimulation is adrenin. It is not an inorganic salt (of potassium, *e.g.*), for it disappears when the cardiac contents are ashed. Like adrenin it is rendered inactive when mixed with eosin and exposed to ultra-violet light (Loewi and Navratil, 1926). The substance derived from smooth muscle has similar properties. Like adrenin, it causes, when conveyed by the blood stream, not only acceleration of the heart, but rise of blood pressure, flow of saliva (in the cat), contraction of the nictitating membrane, the spleen and the pregnant uterus (cat) (Cannon and Bacq, 1931; Rosenblueth and Cannon, 1932). And like adrenin it has its influence increased by a previous injection of cocaine.[31] Despite the resemblances to adrenin, Cannon and Bacq (1931) suggested that the substance derived from smooth muscle when affected by sympathetic impulses be given a special name, "sympathin." Recent experiments by Cannon and Rosenblueth[32] indicate not only that sympathin is different from adrenin, but that there are two kinds of sympathin.

The evidence that sympathin differs from adrenin is found in the difference in the effects of the two substances after ergotoxine. Whereas, under this condition, adrenin causes a pure *fall* of blood pressure, stimulation of the lower abdominal sympathetic chains causes, after an initial slight fall, a prolonged rise; and hepatic nerve stimulation causes a pure *rise*. Both substances, sympathin and adrenin, produce acceleration of the heart; if a dose of adrenin is given, exactly matching the effect of sympathin on the heart, the results on blood pressure are quite opposite in character—the difference, therefore, is attributable to influences on peripheral structures.

Dale[33] has shown that ergotoxine abolishes the action of adrenin on sympathetic vasoconstrictor fibers while leaving vasodilator fibers unaffected. The difference between the actions of adrenin and sympathin, therefore, might be due to different relations to vasodilator systems, *i.e.*, adrenin might affect vasodilators and sympathin might not. This was proved to be true in two ways. Whereas before ergotoxine, sympathin and a moderate dose of adrenin cause contraction of leg volumes, after ergotoxine the *rise* of arterial pressure from sympathin is attended by slight, probably passive, expansion of leg volume, while the *fall* of pressure from adrenin is attended by a marked expansion (*i.e.*, vascular relaxation). Furthermore, if with no ergotoxine, a minimal dose of adrenin is injected into a vein, it induces contraction of the denervated nictitating membrane and an expansion of the volume of the denervated leg; on the other hand, sympathin from the liver region, inducing a similar contraction of the membrane, causes a striking contraction of leg volume. In short, adrenin can induce both contraction and relaxation of smooth muscle, and sympathin, in the experiments mentioned thus far, is shown to induce only contraction.

The question arises, then, is sympathin actually incapable of causing relaxation? To answer this question observations were made on the denervated nictitating membrane as an organ *contracted* by adrenin, and on the denervated non-pregnant cat uterus as an organ *inhibited* by adrenin. When now the nerves to the liver are stimulated the nictitating membrane contracts, but the uterus makes no response. It will be recalled that such stimulation causes, after ergotoxine, a pure rise of blood pressure, as if it has only *contractile* effects. Stimulation of the splanchnic nerves not only has contractile effects, on the blood vessels of the splanchnic area, but also inhibitory effects, on the smooth muscle of the gastro-intestinal tract. The interesting fact then appeared that if the splanchnic nerves are excited, not only does the nictitating membrane contract, but the uterus relaxes. We do not know any region in the body where sympathetic impulses bring about pure relaxation—blood vessels are present which contract. The nerves on the duodeno-hepatic artery, however, are distributed to the liver, where they contract smooth muscle, and to the intestine, where they relax it. When these nerves are stimulated the same effects are seen as when the splanchnics are stimulated —the nictitating membrane contracts, the uterus relaxes. Now if the nerves to the intestine are severed, the same stimulation as before induces only contraction of the nictitating membrane.

From these experiments Cannon and Rosenblueth have concluded that there are two kinds of sympathin —sympathin E, given off from smooth muscle which is excited to contract by sympathetic impulses, and sympathin I, from smooth muscle inhibited by those impulses. Escaping from the cells of origin, sympathin E is carried in the blood stream and is capable of causing contraction in distant smooth-muscle organs which contract in response to sympathetic influences; and sympathin I, analogously, affects smooth-muscle organs which relax.

In an analysis of the hyperbolic curves resulting from the effects on contracted or inhibited smooth muscle, when increasing doses of adrenalin are injected, Rosenblueth[34] was led to infer that a chemical reaction takes place in the cell between the adrenalin

[31] A. Rosenblueth and T. Schlossberg, *Am. Jour. Physiol.*, xcvii: 365, 1931.

[32] W. B. Cannon and A. Rosenblueth, *Am. Jour. Physiol.* (in press), 1933.

[33] H. H. Dale, *Am. Jour. Physiol.*, xxxiv: 176, 1906.

[34] A. Rosenblueth, *Am. Jour. Physiol.*, ci: 149, 1932a.

(A) which enters and a hypothetical substance H, and that the degree of change depends on the amount of AH formed. Because the curves resulting from increasing frequencies of maximal stimuli applied to the sympathetic nerves of the same smooth-muscle organs were identical in character (*i.e.,* rectangular hyperbolas), Rosenblueth[34a] drew the inference that the nerve impulses set free in the cells a mediator (M) which unites with the substance H and affects the responsive agent as AH affects it. In this concept M would be the same as A, and therefore adrenalin would have the same action as sympathetic stimulation.

The experiments just reported require, we believe, the separation of H into two distinct substances, E and I. ME then becomes sympathin E; and MI, sympathin I.

Whether the conclusions derived from stimulation of motor and inhibitory sympathetic nerves can be transferred analogously to motor and inhibitory parasympathetic nerves is questionable. When the chorda tympani is stimulated (Gibbs and Szelöczey, 1932) the perfusing fluid has *inhibitory* effects on the heart and *excitatory* effects on the intestine—a double action which in this case might be expected because of double action of the nerve impulses on submaxillary blood vessels and gland cells. But in the experiments of Engelhart (1931) oculomotor impulses caused *contraction* of the rabbit's ciliary muscle, whereas the substance diffusing into the aqueous humor induced *inhibition* of the tortoise heart. A similar discrepancy occurred in Bain's (1932) experiments on the fluid perfused through the vessels *inhibited* by stimulation of the lingual nerve in the dog; the fluid made the muscles of the rabbit intestine *contract.* In all these experiments, it should be noted, the active substance was obtained by running salt solution through the organs or by adding it to an extract. The substance acetylcholine is well known to be highly unstable. Conceivably any modification of the "vagal substance," for excitation and for inhibition, would not retain its differential feature under such treatment. Or the transfer of vagus stuff from one species of animal to another, as in two of the experiments cited, might be too unphysiological to permit natural results. Or the differential feature might be so closely attached to the reacting mechanism of the cell that it is not free to migrate with the substance which is common to various parasympathetic impulses. Even though the parasympathetic mediator, however, should prove to act differently from the sympathetic mediator, with respect to excitation and inhibition, that would not invalidate the evidence in hand that two types of sympathin exist—in the E and I forms.

[34a] *Am. Jour. Physiol.,* cii: 12, 1932b.

These considerations have interesting bearings on the views expressed by Langley[35] regarding the action of sympathomimetic and parasympathomimetic drugs. He assumed a chemical combination between adrenin, for example, and receptive substances in responding cells. These substances were supposed to belong to two classes—contractile and inhibitory. Langley's receptive substances in smooth muscle would correspond to the substances E and I, here postulated. He did not develop his views with regard to the transmission of nerve impulses—indeed, he did not assume that the impulses evoke locally an adrenin-like substance, as Elliott[36] did. That such a substance is produced when sympathetic impulses influence smooth muscle is indicated (1) by the identity of the curves correlating the responses of smooth muscle with increasing quantities of adrenin and nerve stimulation, (2) by the similarity of the effects of sympathin E and I to the effects of adrenin, and (3) by the similarity of the chemical reaction of sympathin to the reaction of adrenin.[36a] In this view the differences between Langley and Elliott are reconciled and Langley's idea of receptive substances for adrenin is extended to the operation of sympathetic nerve impulses.

The considerations just outlined bear upon a question which has been raised by Parker[37] regarding the source, in muscle cells or nerve terminals, of the neuromimetic humoral agents. The chemical substances which influence chromatophores are of nervous origin—from the eye stalk in the shrimp, and from structures of neural origin, the adrenal medulla and the posterior lobe of the pituitary, in lower vertebrates. Parker has suggested, therefore, that the substance which acts when nerve impulses arrive at an effector cell is a *secretion of the nerve terminals,* and therefore not a derivative of the cell itself. If the nerve twigs distributed to smooth muscle end inside the cell, as the histologists state, a secretion from these minute twigs could not directly enter the blood and thus influence distant organs, but would first mingle with the fluids of the cell. In that case the escaping humoral agent would certainly be in part of muscular origin. Rosenblueth's evidence, that before the responsive mechanism of the cell is affected a chemical union of two substances occurs, is further testimony in favor of a factor provided by the reacting cell. And finally the special character of the substance from contracted and from inhibited cells, sympathin E and I respectively, clearly points to an origin in the muscle cells which respond differently and not in the undifferentiated sympathetic impulses.

[35] J. N. Langley, *Jour. Physiol.,* xxxiii: 374, 1905.
[36] T. R. Elliott, *Jour. Physiol.,* xxxi: p. xx, 1904.
[36a] Z. M. Bacq, *C. r. Soc. de Biol.,* cvii: 1584, 1931.
[37] G. H. Parker, "Humoral Agents in Nervous Activity," p. 55, Cambridge, 1932.

The intermediation of a chemical agent between the nerve and the responsive mechanism in smooth muscle requires, as Loewi[38] has noted, a readjustment of our ideas regarding the mode of action of certain drugs. Atropine, for example, does not paralyze vagal endings in the heart; when the vagi of an atropinized heart are stimulated, quite as much vagus substance is produced as if the heart were not atropinized. The effect of atropine, therefore, is not to prevent the passage of vagal impulses, but to prevent the vagus substance from influencing the responsive mechanism of the cell. Similarly, Cannon and Bacq (1931) found that a dose of ergotoxine which abolished any obvious contraction of the pilomotors did not prevent the production of sympathin E; for the heart was accelerated, by sympathetic stimulation of the pilomotors, quite as much after ergotoxine as before. Again, as Loewi[38] has pointed out, it is commonly supposed that physostigmine sensitizes the heart to vagus stimulation; experiment proves, however, that physostigmine is not directly concerned with vagal impulses, but augments and prolongs the influence of the vagus substance. With increase of knowledge of the rôle of chemical mediators of nerve impulses probably other occasions for modifying ideas of pharmacological action will arise.

The evidence for the existence of two substances, sympathin E and I, resembling adrenin in action but differing from it in discriminative relations to excitatory and inhibitory effects, suggests the possibility of so modifying adrenin by chemical means that it too might be used in a discriminative manner. Thus adrenin E, if made, could be used to stimulate the heart, raise blood pressure, etc., without inhibiting the digestive process. And adrenin I could be employed to relax spasm of the intestine or bronchioles, for example, without raising arterial pressure or increasing blood sugar. Such possibilities render important the attempt to obtain modified forms of adrenin.

[38] O. Loewi, *Internat. ärztl. Fortbildungskursus*, xii: 325, 1931.

HIGH VOLTAGE. II

By Dr. KARL T. COMPTON

PRESIDENT OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY

AFTER this historic survey of electrostatic generators, let me now return to the text of my address, "Necessity is the Mother of Invention." Until very recently there was no compelling need to force physicists to seek ever higher and higher voltages in electrical-generating devices. Their needs were met by existing devices of the electromagnetic type. Within the past dozen years, however, it has become evident that a whole new range of fundamental investigation into the properties of atoms will be opened up by a suitable source of high potentials.

This new inducement may be said to have arisen with Rutherford's discovery that it is possible to transmute one chemical element into another by bombarding it by the fast electrified particles known as alpha particles, which are spontaneously given off by radioactive materials in the process of their disintegration. These brilliant experiments opened up a whole range of new explorations into the structure of the atomic nucleus, and stimulated the imagination of scientists in regard to what might be done if only they had available some more powerful and better controllable source of high-speed missiles to shoot at the atomic nuclei. The alpha particles from radium do have tremendous velocities, but they are relatively few in number and all the radium that could conceivably be gathered together in the world would not produce a stream of electrified particles comparable to that which can be obtained in an ordinary discharge of electricity through a vacuum tube. If only the voltage as applied to a vacuum tube could be made high enough to give the ions in a vacuum tube speeds comparable with or even exceeding those of alpha particles from radium, what a powerful attack could be made upon the nucleus! Not only could particles in billion-fold larger numbers be used, but different kinds of particles could be tried, such as hydrogen-nuclei, helium-nuclei, lithium-nuclei, neon-nuclei and so forth, and these could be given any desired speed up to the maximum limit determined by the highest voltage available. So for the past dozen years, thoughts of scientists have again been turned to means for producing ever and ever higher voltages.

It was to this end that the million-volt installation at the California Institute of Technology was designed. It was also to this end that a system of high potential transformers and condensers was built by Cockcroft and Walton in Cambridge, with which they were the first successfully to disintegrate atoms by means of electrified particles produced from an artificial source and speeded up by an applied voltage. However, the necessities of the case have led to other suggestions for securing high voltages because the inherent limitations of electromagnetic induction devices lead to prohibitive expense and complexity if voltages much above a million volts are sought by such means.