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LOCAL ANESTHETICS[1]

SINCE earliest times, those who have resorted to surgery for the relief of their fellow creatures, have desired to mitigate their procedures by the exclusion of pain. Generally speaking, this has been brought about by a complete abolition of consciousness, whence the term *anesthesia* ("without sensation").

To those cases in which sensation is removed by the application of a drug only at the point of operation is applied the term *local anesthesia;* substances used for this purpose are termed local anesthetics. Some authorities consider this designation inaccurate because during the employment of these substances consciousness is fully retained. They might therefore be described as local *analgesics* ("without pain") but the other term has the sanction of usage.

Historians cite abundant instances of the employment in ancient times of general anesthesia, the oldest being a case of removal of a rib. For this purpose we are told that "the Lord God caused a deep sleep to fall upon Adam," the patient. The commonest of the age-old general anesthetics are alcohol opiates and mandragora, all of which were given separately or mingled with other ingredients.

Local anesthesia, on the other hand, was attempted with comparative infrequency before the last century. Perhaps the earliest authentic description of an approach to this method is that which emanates from the school of Salerno,[2] in the twelfth century. In those days was practised a form of general anesthesia by causing the patient to inhale the vapors of so-called "soporific sponges," the chief ingredients of these being poppy, hen-

[1] Lecture given before the Brooklyn Institute of Arts and Sciences, February 7, 1920.

[2] Cited by Husemann, *Deutsch. Zeitschr. f. Chirurgie,* 1896, 42, 585.

bane and mandragora. As moist poultices the same substances were sometimes laid upon the area where cutting, burning, or some other surgical procedure was to be done. We are told that sensation was thus removed and no pain experienced, but the instance must be assigned with great caution to the category of local anesthesia. The abolition of pain may have resulted only after absorption of these drugs into the circulation, by which means if carried to the brain in sufficient quantity they would, by their central action, produce general stupefaction. From what we know of the action of these substances the remote rather than the local action would be expected. From among such old-time local applications there has come down to us "lead and opium wash," but modern pharmacologists are most skeptical as to the efficiency of opium applied externally.

Prior to the school of Salerno, it is known, of course, that oils and salves were frequently applied to wounds and other painful areas. For example Dioscorides refers to the employment as an eye lotion, of rose oil, a substance about which we shall have more to say later. Of the use of local applications during actual surgical procedure in those days I am aware of no direct evidence.

Many writers refer to the Memphis Stone, of which the oldest descriptions are those of Dioscorides and of Pliny, neither of whom apparently saw it used. Husemann cites conflicting descriptions of its mineralogy. It was called blunt, thick, the size of a pebble; a soft black and hard white variety were applied to the forehead to relieve headache, while an ash-gray variety was said to be of value for snake bites. This talisman and panacea according to both Dioscorides and Pliny was of Egyptian origin and was used to produce local anesthesia, for which purpose it was sometimes powdered and mixed with vinegar. In view of the fact that it was described as a variety of marble the untenable hypothesis has been suggested that the local anesthetic effect was the result of the evolution of carbon dioxide from this mixture when applied to the area of operation.

A second local anesthetic of Egyptian origin and referred to in the sixteenth century by a Dutch physician, Ronsseus, was crocodile fat. In a Latin poem, "Venatio Medica," this author tells us that crocodile fat and a salve of oil and burnt lizard skin were efficient as local anesthetics if applied before cutting or burning.

In the seventeenth century, we are informed of the use of another method of producing local anesthesia, namely the application of cold (for example, by ice and salt mixtures). This was practised by Thomas Bartholinus, who learned it apparently from a distinguished Danish physician, Marc Aurelio Severino. Modern developments of this include the employment of ethyl chloride and other substances of very low boiling point to freeze the skin for minor operations.

The story of modern local anesthetics begins with the isolation in 1860, by Niemann in the laboratory of the German chemist, Wöhler,[3] of the alkaloid cocaine. From Lima, had been brought the leaves of *erythroxylon coca,* a plant which had for years attracted the attention of travelers in Peru and Bolivia on account of its widespread use by the natives as a stimulant. The plant, native to the slopes of the Andes, is a shrub attaining a height of about six feet, with bright green leaves, similar in size and shape to those of tea, which are rapidly replaced when picked. The annual consumption of these leaves in South America is now estimated at one hundred million pounds.

The "coqueros" or chewers of coca leaves had ascribed wonderful properties to them, not only of abolishing hunger, fatigue, bodily discomfort, etc., but also of psychic stimulation of various sorts. When put to the test in Europe these claims were but poorly substantiated owing, according to some, to deterioration of the properties of the leaves in transportation, but probably more to a difference in the subjective conditions of the test; that is, the European investigators were probably neither as hungry and fatigued nor con-

[3] Wöhler, F. W., *Ann. der Chem. u. Pharm.*, 1860, 114, p. 213.

stitutionally as emotional as the "coqueros." Nevertheless sufficient nervous stimulation is derived to render cocaine a dangerous habit-forming drug.

After the manner of chemists with a new product, Wöhler tasted cocaine and noted (to translate literally), that "it is bitter and exerts upon the tongue nerves a characteristic effect in that the point touched becomes temporarily numb, almost without sensation." Twenty-four years elapsed before the significance of this finding was fully appreciated; Koller, a Viennese oculist, in 1884 introducing it as a practical local anesthetic for the eye. In the meantime, however, Parisian workers had noted anesthesia of the tongue when the leaves were chewed with alkali (DeMarle, 1862); and Moréno y Maiz (1868), had suggested the employment of the drug as a local anesthetic. A number of fundamental pharmacological facts about cocaine were demonstrated by Von Anrep[4] (1880).

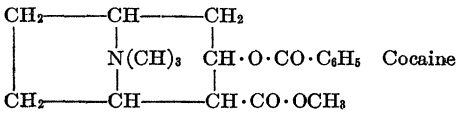
From the eye clinic the use of the drug spread to laryngology and rhinology and later to general surgery. As it is typical of a large class of local anesthetics its action may now be somewhat more fully detailed.

Cocaine is classed as a "general protoplasm poison," since relatively small amounts exhibit the power to interrupt or suppress the life process both of lower and higher organisms. In mammals it attacks nerve tissue in particular and there are acute and chronic types of brain poisoning, the latter, of course, being illustrated in the widespread abuse of the drug. Acute poisoning (motor excitement and high temperature followed by convulsions) has been noted in all attempts at anesthetization of animals by intravenous injection or other means of introducing the drug into the general circulation. The local or peripheral action can not be obtained by such methods.

The portions of the nervous system upon which the action is useful are the nerve trunks and their sensory endings, and as may be judged from the above, one problem of the surgeon is to keep the substance limited as far as possible to these regions. On the nerve trunks it has a selective action in blocking afferent or sensory impulses much more readily than efferent or motor impulses, both of which are carried by the same bundle of nerve fibrils. Its selective action is further illustrated by the abolition, upon application to the nerve ends, of pain and touch sensations, while the perception of heat and cold remains uninterrupted. Again, on the tongue, in addition to touch and pain, the perception of "bitter" taste is completely eliminated, yet those sensations which we describe as "sweet" and "acid" taste are still dimly perceived, while the presence of salt may still be appreciated as well as ever.

That cocaine is not an ideal local anesthetic can be readily appreciated. Aside from its disadvantages as a habit-forming drug and the possibility of the development of toxic symptoms if unskillfully employed, there are minor objections which include the possibility of injury to the tissues or interferences with natural processes of repair if given in too concentrated a solution and the fact that solutions if sterilized by boiling undergo some decomposition.

Since these facts began to receive attention the production and testing of synthetic substitutes for cocaine has been a nearly continuous performance. As the structural formula of the alkaloid shows, it is the methyl ester of benzoyl ecgonin:

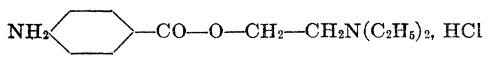


Its decomposition products are methyl alcohol, benzoic acid and the tropine-like base ecgonine. Investigations by Filehne, Paul Ehrlich, and others, were undertaken to determine in which of these chemical groups or in what combination of radicals the anesthetic virtues resided. The benzoic acid radical was soon indicated as being of importance; for example, neither ecgonin nor methyl ecgonin were found at all like cocaine in their action. On the other hand the isomer of cocaine in which the methyl and benzoyl radicals were

[4] Von Anrep, B., *Pflüger's Archiv. der Physiologie*, 1880, 21, 38.

made to exchange places, exhibited no local anesthetic properties; when, however, the benzoic acid radical was replaced in the cocaine structure by other homologous acids, substances with cocaine-like action were evolved.

Einhorn, who had earlier been associated with Ehrlich's work, introduced as a local anesthetic orthoform. This is the methyl ester of an oxy-benzoic acid modified by the introduction of an amino group to replace the very complicated base ecgonine. This substance, while poorly soluble, has found a place in surgery as an anesthetic dusting powder. Einhorn[5] next modified the orthoform grouping in such a way as to produce more soluble compounds, but achieved his greatest success by the introduction of the "alkamine" esters of benzoic acid, notably procaine (known also by the trade name of novocaine):



Procaine.

In other synthetic compounds (stovain, alypin, and B-eucaine), no amino group appears on the benzene nucleus. In still another series of compounds, the benzoyl group has by an intervening side-chain been attached to the nitrogen of the ecgonine molecule. This work was reported recently by Wichura[6] (1918) and one of the compounds, apparently giving promise, is known as eccain.

Another natural alkaloid has been obtained from the small coca leaves of Java. This substance, tropacocaine, was found by Dr. Arthur P. Chadbourne[7] (1892), of Boston, to possess valuable anesthetic properties. Similar in structure to cocaine (of which it is in many ways the equal) it contains pseudotropine in place of the ecgonine radical.

In the group of antipyretic drugs also are found substances of value as local anesthetics, although these are chemically quite unrelated to cocaine. Among them are holocaine, a phenacetin derivative, and quinine, which is used in combination with urea. In 1913, Morgenroth showed that certain quinoline derivatives have a similar action, including a group of substances which also give promise of a specific value in the treatment of pneumonia. Antipyrine may be included in this and in the following group.

In 1888, Liebreich[8] called attention to the fact that a large number of substances are capable of producing "anesthesia dolorosa." This term is applied to the phenomenon of smarting followed by loss of sensation. Among the substances which he enumerated were sodium bromide, ammonium chloride, lead acetate, ferric chloride, resorcin, and even the glucosides saponin and napellin. Carbolic acid affords the most conspicuous example of this type, its action culminating as is well known in the death of tissue.

In spite of the untoward effects of carbolic acid, which is an aromatic alcohol, certain closely related aromatic side-chain alcohols are now yielding much promise of practical value. Dr. David I. Macht,[9] of Baltimore, the pioneer in this field, a few years ago noted the anesthetic effect of benzyl alcohol upon the tongue, demonstrated its highly innocuous character, and was instrumental in introducing it into surgery.

In our laboratory three similar side-chain aromatic alcohols have been tested, chiefly by Dr. Axel M. Hjort,[10] whose work has been aided by the Committee on Scientific Research of the American Medical Association. As will be seen from the following summary of Dr. Hjort's findings, two of these, rose oil and benzoyl carbinol, possess a high degree of anesthetic efficiency combined with a low degree of toxicity.

[5] Einhorn, *Liebig's Annalen*, 1908, 359.

[6] Wichura, Wilhelm, *Zeits. für Exper. Path. and Therapie*, Vol. 20, p. 1.

[7] Chadbourne, A. P., *Brit. Med. Jour.*, 1892, II., 402.

[8] Liebreich, *Verhandl. de 7 Kongr. f. inn. Medizin*, 1888, S. 245.

[9] Macht, D. I., *Jour. Pharm. and Exp. Therap.*, 1918, XI., 263.

[10] Hjort, A. M., and Kaufmann, C. E., *Proc. Soc. Exp. Biol. and Med.*, January, 1920.

	Formula	Minimal Lethal Dose White Mice. Mgs.	Minimal Effective Anesthetic Concentration (Rabbits' Cornea) %	Minimal Effective Anesthetic Concentration in (Human Skin) %
Benzyl Alcohol..		50	1.25	1/30
α Phenethylol ..		20	0.75	1/40
β Phenethylol (rose oil)		40	1.00	(1/40)
Benzoyl Carbinol		40	0.50	1/40

Rose oil, or β-phenethylol, it will be remembered, was one of the preparations mentioned by Dioscorides as an eye wash; roses apparently were considered effective in many diseases at that time. Blondel[11] (1889) describes the use of essence of rose for its stimulant properties, its action when taken by mouth not differing essentially from that of other volatile oils. This substance as well as its isomer α-phenethylol are liquids, the latter exhibiting greater toxicity, the probability of which we had deduced from the fact that it contains an asymmetrical carbon atom. Benzoyl carbinol is a solid at ordinary temperatures and of all the group has yielded the most promising results.

While it is more practicable to make the detailed toxicity tests upon mice, it is important to control the results by tests upon higher mammals. In dogs it was found that, like benzyl alcohol, rose oil and benzoyl carbinol fail to cause more than the most transitory symptoms when injected rapidly into the veins in doses of 200 mgms. per kilo. This contrasts very favorably with the toxicities of the commonly used local anesthetics which have been carefully determined by Drs. Robert A. Hatcher and Cary Eggleston,[12] of New York. These investigators found, for example, that by rapid intravenous injection in cats 40–45 mgms. per kilo of procaine or 15 mgms. per kilo of cocaine are fatal. Thus the benzyl alcohol and rose oil appear at least five times as safe as procaine.

The toxicity of benzoyl carbinol in comparison with a series of common local anesthetics may be illustrated graphically by the following adaption of Eggleston and Hatcher's diagram:

Fatal Dose. Mgms. per Kilo	Relative Toxicity
> 200.....	Benzoyl Carbinol, benzyl alcohol, etc.
40– 45.....	Procaine
30– 35.....	Nirvanine
25– 30.....	Stovaine
18– 22.....	Tropacocaine
20.....	Apothesine
15.....	Cocaine
10–12.5.....	Beta-Eucaine
10.....	Alypine and Holocaine

Hatcher and Eggleston point out that with local anesthetics, as with other drugs, the degree of toxicity may depend upon the rate of injection or absorption into the circulation. They show that slow injection allows time for destruction by the liver.

On the basis of the results in dogs it would appear that a man could safely tolerate the throwing of solutions containing one half ounce of pure rose oil or of benzoyl carbinol directly into the circulation; used as a locally applied anesthetic, therefore, poisoning would scarcely be anticipated.

For "surface" or "mucous membrane" anesthesia the rabbits' eye is a valuable test object. Anesthesia of the surface of the rabbit cornea may be identified by the failure of the animal to respond by a wink when the center of the eye is touched. Schlüter has published interesting experiments in which after a drop of local anesthetic was instilled into the eye the threshold for touch sensation was followed by means of hairs of different weights. He showed that when solutions of equal strength are compared, procaine is quite inferior to cocaine as a surface anesthetic. Benzoyl carbinol, as shown below, is particularly efficient in this respect, yielding complete anesthesia of the cornea in 0.5 per cent.

[11] Blondel, R. E., Thesis, "Les Produits Odorants des Rosiers," Paris, 1889.

[12] Eggelston, C., and Hatcher, R. A., *J. Pharm. and Exp. Ther.*, 1919, 13, 433.

concentration. This is the first of the aromatic side-chain alcohols to equal cocaine as a surface anesthetic.

The following diagram (adapted from Sollmann) illustrates the comparative efficiency of phenolic side-chain alcohols and the commonly used surface anesthetics:

Minimum Anesthetic Percentage	Relative Efficiency for Surface Anesthesia
0.5	Cocaine, holocaine, benzoyl carbinol
0.75.....	α-phenethylol
1.0	Beta-Eucaine, rose oil
1.25.....	Benzyl alcohol
2	Tropacocaine, alypin, quinine-urea
4	Apothesine
8	Novocaine
10	Antipyrine

The intracutaneous method of testing local anesthetics was introduced by Hoffmann and Kochmann (1914) and consists in the production of wheals resembling mosquito bites, by driving the anesthetic substance in between the layers of the epidermis, under pressure, with the hypodermic syringe. The subject of the experiment, who is, of course, prevented from watching the procedures, is required to give a signal every time he perceives the touch of a straw tipped with absorbent cotton. None of our phenolic alcohols are found irritating by this method and all destroy sensation in a concentration of about 1/40 of 1 per cent., as low a strength as has proved sufficient for any known anesthetic substance.

This is illustrated by the following diagram (also adapted from Sollmann):

Minimum Anesthetic Percentage	Relative Efficiency for Intracutaneous Anesthesia
1/40	Benzoyl carbinol, rose oil, α-phenethylol
1/30–1/32.....	Benzyl alcohol, cocaine, novocaine, tropacocaine, alypin
1/16	Beta-eucaine
1/8	Quinin-urea
1/4	Apothesine, antipyrine, K_2SO_4

Dr. Arthur D. Hirschfelder,[13] of Minneapolis, and his collaborators, have recently announced the results of experiments with similar side-chain aromatic alcohols. A number of these are based upon the salicylic acid radical. From Hirschfelder's results it is obvious that saligenin in 2 per cent solution is likely to prove a very valuable anesthetic. In his hands this has given a 28–45 minute human subcutaneous anesthesia and has completely anesthetized the mucous membranes of the eye.

Several benzyl alcohol homologues, therefore, which are more stable than benzyl alcohol itself, better surface anesthetics than procaine, and at least five times less toxic, and which further are presumably very unlikely to become habit-forming drugs, are now receiving practical trials.

The two above described tests, surface and intracutaneous, represent the most important of the procedures employed by the surgeons. Clinically, there are five main varieties of local anesthesia, namely, (1) surface, (2) terminal, (3) regional, (4) spinal, (5) venous.

1. To anesthetize mucous membranes such as the linings of the eye, nose, and throat, the solution requires only to be painted upon the surface.

2. To anesthetize the nerve ends in the skin, however, it is necessary that the drug be injected into the skin by means of the hypodermic needle. This is owing to the fortunate circumstance that the living layers of the epidermis are quite impermeable to most solutions with which they may come in contact. Obviously where deper incisions are to be made, subcutaneous injections must follow. Schleich[14] modified the method of terminal anesthesia very acceptably by showing that if hypotonic solutions be injected under pressure to the point at which the tissues become rigid, the anesthetic may be reduced in concentration. This is in accord with findings that either hypotonic or hypertonic solutions of salts tend of themselves to produce local anesthesia, apparently owing to the fact that in swelling or shrinking respectively,

[13] Hirschfelder, A. D., A. Lundholm, H. Norrgaard, American Chemical Society, Division of Biochemistry, September 4, 1919.

[14] Schleich, C. L., "Schmerzlose Operationen," Berlin, 1906.

the vital processes of the cells are partly interfered with.[15]

3. To anesthetize the area supplied by a given nerve, it is only necessary to inject a sufficient amount of solution directly into the nerve trunk. This often effects a great saving of labor and material. The larger nerve trunks were first blocked in this manner by Dr. Harvey Cushing, of Boston.

4. Anesthetics are occasionally injected under the sheath of the spinal cord itself. Spinal anesthesia was introduced in 1885 by Dr. J. Leonard Corning, of New York, in the same year in which Dr. Halsted, of Johns Hopkins, began his pioneer work in cocaine surgery. Many of you may recall that in the closing years of the last century a substance known as stovaine, belonging to the orthoform group, was widely heralded in connection with spinal anesthesia.

5. To produce venous anesthesia an area is made bloodless by tight bandaging and the anesthetic solution injected backwards into the vein which ordinarily transports blood away from that area.

Certain substances have been tested as adjuvants, to be added to local anesthetic solutions. Among these epinephrin has been found extremely valuable and is universally employed, while sodium bicarbonate and potassium salts are deserving of mention.

For terminal anesthesia procaine is injected in solution with epinephrin, the active principle of the adrenal gland. A concentration of 1–100,000 of the latter suffices to blanche the tissues by contracting the small blood vessels with which it comes in contact. This serves two useful purposes, to make the operation practically bloodless and to prevent any rapid carrying off of the drug into the circulation.

[15] Terminal used in combination with general anesthesia is believed to rob the latter of some of its disadvantages, for while the patient, narcotized by ether, chloroform, or nitrous oxid, does not perceive the afferent nerve impulses set up by surgical procedures, these reach the central nervous system nevertheless and may contribute to the untoward condition known as "shock." Local anesthesia tends to prevent the transmission of such impulses. (Crile.)

Sodium bicarbonate as an adjuvant to local anesthetics was suggested by Gros[16] (1910), who believed that bringing the alkaloids into their basic forms, would aid them in penetrating the tissues. Dr. Torald Sollmann,[17] of Cleveland, has found that it does in fact enhance the action of such alkaloids when they are applied to mucous surfaces. On the other hand, he denies that it has any special value in terminal anesthesia.

With regard to potassium salts it may be mentioned, that Hoffmann and Kochmann[18] (1912) claimed that potassium sulphate powerfully potentiates the action of procaine in intracutaneous anesthesia. Dr. Sollmann's results conflict with this claim as do also the results of a number of unpublished experiments which I have made in association with Professor Bernard E. Read, of Peking. In short, salts of potassium, which in fairly high concentration produce a certain amount of intracutaneous anesthesia, when given in combination with such a substance as procaine, yield a result representing merely the algebraic sum of the results obtained by giving the two substances separately.

The theory of action of local anesthetic drugs has not yet reached a satisfactory state. Gros believes that their anesthetic power runs parallel to the amount of free base which is present and that esters such as cocaine and procaine must therefore be hydrolyzed before anesthesia can take place. The extent of the anesthesia would therefore depend upon the degree of hydrolysis of the drug taking place in the tissues. The new findings concerning substances of the benzyl alcohol series show that phenolic alcohols contain all that is essential to local anesthetic action and that for introduction into the field of operation it is not necessary to mask them as esters.

Exactly what happens to the nerve tissues when brought into contact with a local anesthetic drug has not been determined.

[16] Gros, O., *Arch. f. exp. Pathol. u. Pharmakol.*, LXIII., 1910.

[17] Sollmann, T., *J. A. M. A.*, January 26, 1918, p. 216.

[18] Hoffmann, A., and Kochmann, K., *D. M. W.*, 1912, 38, 2264.

We can say, however, in view of the results of work initiated by Dr. A. P. Mathews, that the vital processes in nervous tissue become retarded. This is indicated by the lowered carbon dioxide production exhibited by a nerve exposed to cocaine. Niwa[19] (1918) states that "there is a close relationship between the rate of nerve metabolism and the state of excitability of the nerve" and that "anesthesia in general is probably brought about by interference with the tissue metabolism." This does not differ greatly from Verworn's theory of anesthetic action.

While practise in this case, pending the perfection of theory, proceeds with a tolerable degree of satisfaction, we still await the demonstration of the ideal local anesthetic. This form of anesthesia, however, is extending its usefulness through an ever widening field. Few are the types of major operations which can not now be successfully conducted under its sole employment, always provided that numerous external conditions are satisfied. Among the advantages ascribed to it when thoroughness of operative procedure is not thereby sacrificed are its high degree of safety and rapidity of induction, the exclusion of shock and often of after-pain, the necessity for fewer assistants, the shortening of convalescence, and the absence of post-anesthetic complications. An additional factor of importance is the better mental attitude with which many patients approach such a procedure rather than an operation involving the surrender of consciousness. Some enthusiasts go so far as to say that many an operation assumes the character of a social rather than a surgical occasion, the patient perhaps smoking throughout and enjoying a good meal directly thereafter.

While we are not so advanced that serious ceases are made thus attractive, the day of ideal surgery will doubtless be hastened by the replacement of older for better local anesthetics.

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[19] Niwa, Shuichi, *Jour. Pharm. and Exp. Therap.*, 1919, 12, 323.

PHENOMENA IN THE ULTRA-VIOLET SPECTRUM, INCLUDING X-RAYS

At the recent St. Louis meeting of Section B, of the American Association for the Advancement of Science, there was held a symposium devoted to a comparative discussion of the phenomena involved in the ultra-violet "light" and "X-ray" spectra. The following abstracts of the papers have been prepared by the authors:

A. Quantum Emission Phenomena—Radiation, by David L. Webster, Massachusetts Institute of Technology.

This paper contained a review of the laws of excitation of radiation by electron impact in the best known cases in X-rays and light, in which it appeared that the most essential difference is the existence in light of the so-called "single-line spectrum" which is unknown in X-rays. The phenomena are explainable on any theory of stable electron positions, such as the Bohr theory, if we assume: (1) that in the normal atom all positions involved in X-ray production are full (Kossel), and (2) all positions above the one corresponding to the series term 1.5S are empty (Van der Bijl).

Such theories are very unsatisfactory for absorption phenomena, especially since absorption is a continuous process but results in the production of photoelectrons, each with an absorbing oscillator and a gradual accumulation up to the value required for the photoelectron. If energy is thus stored it seems probable that it would be available to help in the production of X-rays or light by impact, and to produce other effects to be expected from it. But no such evidence of it can be found. The storage hypothesis is made only because it is demanded by the law of the conservation of energy. But this law has been observed only statistically, and the best way to reconcile these phenomena of electron impact with other radiation phenomena seems to be to assume that the law holds only statistically and does not apply to every oscillator at every instant.