Physiology, the servant of medicine : chloroform in the laboratory and in the hospital / [Augustus D. Waller].

PHYSIOLOGY
THE SERVANT OF MEDICINE

A. D. WALLER, M.D., LL.D., F.R.S.

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(CHLOROFORM IN THE LABORATORY AND IN THE HOSPITAL)

BEING THE HITCHCOCK LECTURES FOR 1909 DELIVERED AT THE UNIVERSITY OF CALIFORNIA, BERKELEY, CAL.

BY

AUGUSTUS D. WALLER, M.D., LL.D., F.R.S.

(Director of the Physiological Laboratory of the University of London)

Was kann ich wissen?
Was soll ich thun?
Was darf ich hoffen?

KANT

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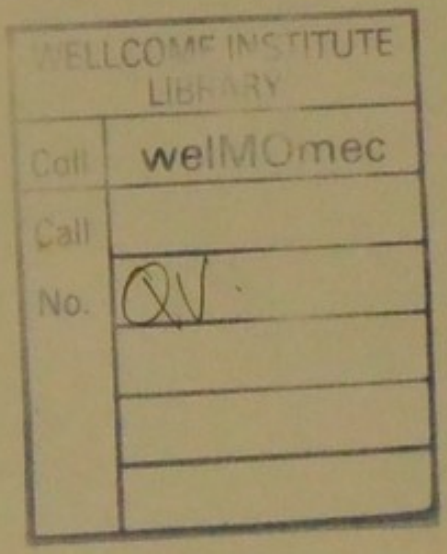

PREFACE

THE general title of these Lectures is intended as an acknowledgment—their specific title as an indication. They contain indeed no historical review of the relations between Physiology and Medicine, but only some fragments of Physiology of which I have sought to emphasise the application to Practical Medicine, and among which the study of chloroform has been a constantly recurring note.

They were delivered in October 1909 at the University of California, in accordance with the terms of the will of the late Josiah H. Hitchcock, providing "for the delivery of lectures upon scientific and practical subjects, but not for the advantage of any religious sect nor upon political subjects." And it has been in the endeavour to fulfil as far as possible the objects of this bequest, that I have not restricted myself to the purely physiological bearings of the subjects dealt with.

I have followed this lead all the more willingly by reason of my own conviction that, while it is essential that scientific inquiry should be pursued for its own sake without regard to immediate utility, its ultimate justification consists in its practical application to the service of Mankind. It must answer the second of Kant's three questions, "Was soll ich thun?" as well as his first question, "Was kann ich wissen?"

In no case is this more clearly apparent than in the relation of Physiology to Medicine. Physiology must be studied for its own sake, but the Physiologist whose immediate motive is the "want to know," may not deny his debt of service to the community of which he forms

part, and whose services he enjoys. And the channel through which he can best pay some part of that debt lies first of all through the service he may be able to render to the practice of Medicine—to the knowledge and power of the Physician, whose immediate motive is the "want to help."

I have given particular prominence in these Lectures to our physiological knowledge of Anæsthetics. The Fifth Lecture is exclusively devoted to the practical applications that are derived from that knowledge. I have relegated to the Appendix technical laboratory directions, and data that accompanied the Lectures in the form of diagrams.

I have also given in the Appendix half the subject-matter of a more general address delivered to the University of California; the second portion of that address consisted in a brief sketch of the constitution and character of the University of London, and I have substituted for that necessarily most imperfect sketch of what exists in London, the outlines of what I hope may be brought into existence as an outcome of the labours of the Royal Commission on the Organization of the University of London.

On the purely scientific side, the present series of Lectures embodies the principal results of my own laboratory work during the last seven years at the University of London. In this respect they are in continuation of two previous series of Lectures, viz. Lectures on Animal Electricity (1897), and Lectures on the Signs of Life (1903).

AUGUSTUS D. WALLER.

Physiological Laboratory, University of London, South Kensington, April 1910.

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LECTURE I

I BEG you to believe that in prospect of the honourable task laid upon me by the University of California, I have not failed to pass through the preparatory searchings of mind that are its due.

Although it has so far been impossible to me to crystallise out into their simplest shape as written images the facts and thoughts that I hope to lay before you—and, indeed, had I done so, it would be impossible that I should now present them to you in that shape—I beg you to believe that, except as regards the preparation of an actual manuscript, I have not neglected that necessary setting of one's mind in order, in default of which no man is entitled to lay claim to hearing.

So I have done my best, and shall spare no pains to justify your invitation to lecture here.

Let me at once—and, indeed, I already feel that this will not be difficult—imagine that I am at home, in my own laboratory, with five lectures in front of me.

I should stake out roughly five definite "claims," to include at least five dominant ideas, five representative concrete experiments, five definite practical conclusions; and round each of those five fixed points I should group what seemed to me to be the best of my own knowledge,

and the most likely to lead to further knowledge. And I should be very disappointed indeed, if in five days' washing and sifting of picked stuff, my pannikin did not sometimes show "colour."

Let me briefly sketch out our plan of work. These are its five chapters—

In this *First Lecture* I shall at once show you an experiment on an isolated muscle by which you shall judge for yourselves whether it is true that chloroform is forty times as powerful as alcohol. I shall develop before you what I may characterise as the two languages of muscle. I shall describe a general method of experimental procedure, and, I hope, make good the claim that the systematic examination of the electrical signs of life yields valuable information. In this connection I shall say something about the electrical effects of the human heart, because I have been specially asked to do so. And I shall tell you the story of a "tortured" bulldog.

For *Lecture II* the headings are :—The language of isolated nerve, and what it has to say about ether and chloroform. An experiment to convince you that an electrical response is a sign of life. The normal electrical response of nerve ; its positive and negative components. The effects of carbonic acid on nerve. The production of carbonic acid by nerve.

Lecture III.—The effect of hellebore on the electrical response of nerve. The double chemical movement of excited nerve. Effects of the aconite alkaloids.

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blaze. The language of green leaves, and of a flower petal. The photo-electrical response of the retina, and of green leaves. The electrocution of vegetables. Electrical seed-testing. The last sign of life and the first sign of life. The anæsthesia of vegetables.

Lecture V.—Anæsthesia—its pricelessness and its price. Shall we choose chloroform or ether? The arithmetic of chloroform vapour. The chloroform balance. The death-roll of chloroform. Statistics. Chloroform as it is used in the Laboratory and as it should be used in the Hospital.

That is a rough prospective sketch, that I shall assuredly not carry out point for point in its entirety as I should wish to do, that will be deflected in this or that direction as we progress from point to point, but that after all will, I hope, have fulfilled its aim, and shown "colour" in some of the day's washings—"colour" that should whet appetite and industry in our further pursuit of knowledge. But let us not pursue metaphors. All that I wish to say further in introduction of these lectures is this: Although I know in a general sense what I intend to do and say, but cannot write down word for word and step for step the precise path that we may be drawn into, I fully intend to submit its results to your criticism in their printed as well as spoken form, since I could hardly be held to have fulfilled my duty here until I had condensed the spoken into the written statement. For, after all, the printed statement is the only permanent testimony of work done. We think and search and think again, we bring a portion of our thoughts to the tests of the laboratory, we fill our note-books, we take the essence of our note-books and we write a paper—many papers—in dry, technical language; after much thought and work and many papers, we are perhaps learned enough to

tell a simple story. Some of our spoken stories may be worth printing. Some of our printed stories may be worth reading.

Our task as Physiologists is to study the "signs of life" in Animals, in Plants, in their isolated organs and tissues.

"Are you alive?" "How much are you alive?" are the two chief questions set by experiment to any living (or dead) matter that has aroused our curiosity—be it an excised nerve or an excised muscle, a blade of grass or the seed of a plant.

Let us take at once an isolated *muscle*, since that is the most familiar possible object in physiology, and let us see what it can have to say to us.

We know very well already that in answer to our question, "How much are you alive?" the muscle contracts more or less, and *pari passu* exhibits a larger or smaller electrical change. It speaks at least two languages—a mechanical language which is very obviously its own, and an electrical language which is somewhat less obvious and which it shares with other tissues, and indeed, as far as concerns us in the laboratory, is practically the only language in which such other tissues can answer us at all. An isolated nerve, for instance, or a piece of skin, can tell us how much it is alive only by its electrical response.

I want at once to fix two principles in your mind in connection with this experiment—

1. The electrical response is not the consequence of the mechanical response, but both responses are the outward and visible signs of an underlying chemical change.

2. The electrical and the mechanical responses run a parallel course. Both changes give practically the same numerical answer to the question, "How much have you altered?" and we may set the muscle to give us informa-

tion in whichever of the two languages happens to be the more convenient, using for its mechanical language a myographic lever, for its electrical language a galvanometer.

I should like this principle to be very distinctly before our minds, and am therefore illustrating it by a simple experiment. The same muscle is connected with a myograph and with a galvanometer. I stimulate it to contract. You see with each twitch of the muscle a galvanometer deflection. As magnified on the screen the contraction is two feet high and the deflection is two feet long. I tetanise the nerve so as to fatigue the muscle, and repeat the trial. The contraction is rather more than a foot high and the deflection is rather more than a foot long. I tetanise again, and now the contraction and the deflection are a good deal less than a foot. That will do to fix the fact that we may use either mechanical or electrical indications to gauge the state of the muscle. And of course while there are other changes, as of heat and of carbonic acid, obviously neither of these changes can supply anything like as convenient a measure of the alterations taking place in the state of a muscle.

No doubt the myograph or muscle-writer is familiar to all here, so I shall not describe it, but simply use it at once to get an answer to a question for which it is convenient to make the muscle use its mechanical language.

I want to know, let us say, how much a muscle is affected by alcohol. So I put it up as you see, test its contractility in a bath of normal saline to see how much it contracts normally, then test its contractility in a bath to which a definite amount of alcohol has been added, and finally, when, as will presently occur, the contractility has fallen to zero, test it again from time to time to see whether, and how quickly, and how much, the muscle

recovers contractility when it is removed from the influence of alcohol.

I am not a temperance lecturer. Of course, like most people, I have more or less definite ethical notions about drink and drinks, but as a student of science I have no

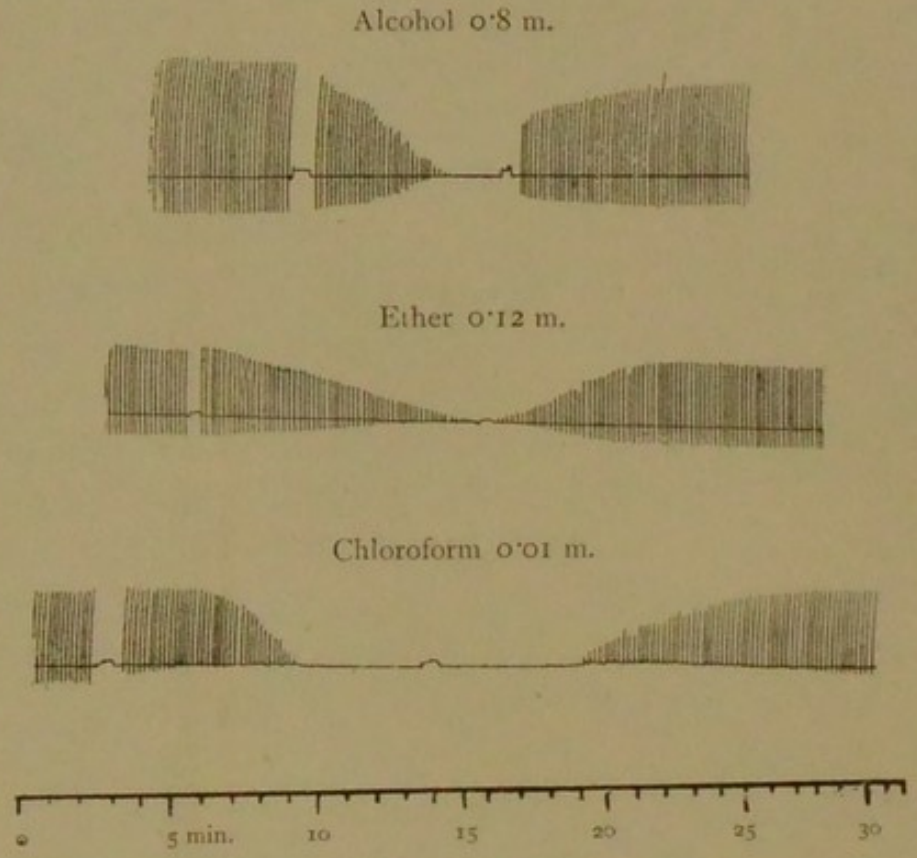


FIG. 1.—Effect on muscular contraction of—

Alcohol . .	5 c.c. per 100 (0·8 m.).
Ether . .	1 c.c. per 100 (0·12 m.).
Chloroform .	0·08 c.c. per 100 (0·01 m.).

Each record is composed of three groups of contractions: (1) in normal saline; (2) in medicated saline, gradually abolished; (3) in normal saline, gradually recovering.

notions whatsoever. All I want to know now and here is "how much" alcohol interferes with the vitality of muscle.

I shall have a good deal to say in a later lecture about anæsthetics—ether and chloroform namely. I want to know more about chloroform, since, unfortunately, a good

many lives are lost every year, because we, the doctors, know so much less than we ought to know about chloroform and its safe management.

The alcohol bath to which the muscle was submitted a short time ago was of a definite strength—46 grammes per litre. In order to compare the power of chloroform with that of alcohol, let us make a similar experiment with the same, or with a different muscle, submitted to a chloroform bath. Knowing that chloroform is much more powerful than alcohol, we shall use a much more dilute bath, viz. a 1·2 gramme per 1000 solution of chloroform in saline, $\frac{1}{100}$th of the alcohol strength counting by molecules, about $\frac{1}{40}$th counting in grammes.[1] At these concentrations the two solutions will produce not very unequal effects upon the muscular contraction, and I shall therefore be entitled to say that chloroform is about forty times as powerful as alcohol.

If our time were unlimited, I might make yet another experiment, taking a 7·4 per 1000 solution of ether in saline, *i. e.* $\frac{1}{10}$th of the strength of the alcohol solution, counting as before by molecules, and you would probably have witnessed a rather less rapid effect in this case than in that of either of the other two solutions ; ether at that concentration (decimolecular) is not quite strong enough to bring about as much effect on the muscle as did chloroform at centimolecular or alcohol at molecular concentration. Nevertheless, the inequality is not so great as to forbid us from thinking about a molecule of chloroform as being ten times as powerful as a molecule

[1] The molecular weight of ethyl alcohol, C_2H_5OH, = 46. A solution at 46 grammes per litre is a solution of molecular concentration. The molecular weight of chloroform, $CHCl_3$, = 120 nearly. A solution at 1·2 gramme per litre is a solution of centimolecular concentration. The molecular weight of ether, Et_2O, = 74. A solution at 7·4 grammes per litre is a solution of decimolecular concentration.

of ether and a hundred times as powerful as a molecule of alcohol.

But you have seen enough of the method to be enabled to appreciate its results, and to realise what an easy means it places in our hands for obtaining a physiological comparison and measurement of alcohol and anæsthetics, and of a host of other medically important substances. There is nothing particularly novel about the method, and I cannot lay claim to the slightest credit as having originated it; I have merely systematised it and plodded with it for a year or two, and I shall probably continue to do so only until it becomes received among ordinary routine methods of systematic inquiry. If any one here wishes to take it up he might find it worth while to consult a recent paper of mine that contains a description of apparatus and results in fuller detail than can be suitably given now.[1]

I should like to call your attention to the fact that each complete experiment is in the strict sense of the term a "crucial experiment." The apparatus is double. A pair of muscles is excited by induction shocks at regular intervals traversing the two muscles in series. The action of two solutions, *x* and *y*, is to be compared.

During the first half of the trial A is in *x*, B in *y*, and we have a simultaneous comparison on two different muscles of the effect of *x* with that of *y*. During the second half of the experiment the solutions are transposed, and we have a second simultaneous comparison of our two solutions, but with A in *y*, and B in *x*. And, lastly, comparing on the completed record the four parts of which it is composed, we have also two successive comparisons, each on the same muscle. A in *x* followed by A in *y*; and B in *y* followed by B in *x*. That has

[1] Note 1, Appendix.

been a clumsy string of words with which to describe an *experimentum crucis*—in the correct sense of that term as used by Bacon. Our crossed or crucial series has been—

$$\begin{array}{c|c} Ax & Ay \\ By & Bx \end{array}$$

Here, finally, is a tabular summary obtained from a considerable number of such "crucial experiments," setting out in round numbers the physiological equivalence of alcohol, ether, and chloroform.

	By molecules	*By weight* (approximate)	*By volume* (approximate)
Alcohol . . .	100	40	75
Ether	12	8	15
Chloroform . .	1	1	1

Viz. 1 molecule chloroform = 12 molecules ether = 100 molecules alcohol.
1 gramme chloroform = 8 grammes ether = 40 grammes alcohol.
1 c.c. chloroform = 15 c.c. ether = 75 c.c. alcohol.

To say from these numbers how much stronger chloroform is than ether or than alcohol, we had better take their reciprocals to form a table of the relative physiological powers of the three drugs, as follows—

	By molecules	*By weight*	*By volume*
Alcohol . . .	1	1	1
Ether	8	5	5
Chloroform . .	100	40	75

Thus, to talk by volume, a cubic centimetre of ether is five times as powerful as a cubic centimetre of alcohol, and a cubic centimetre of chloroform is seventy-five times as powerful.

So much for *isolated* muscle. We may be satisfied, may we not, that in the language of contraction an isolated

muscle can be made to tell us very clearly and very simply facts about drugs that are of very immediate interest to us. It is surely worth while to learn that a molecule of chloroform is about a hundred times as powerful as a molecule of alcohol. And I hope you will agree with me that it will be worth while to return to this very practical matter in a future lecture.

THE ELECTRICAL ACTION OF THE HUMAN HEART.—I should like now to invite your attention in a different direction, though still in connection with the case to which I have just spoken. The electrical expression of the activity of muscle finds a remarkable—perhaps its most remarkable—illustration in the electrical changes that accompany the contractions of the heart; and from the experiment you have just witnessed upon an isolated muscle, you will, I think, be very easily led to see how it is that the action of the heart in its natural situation, in any one of ourselves, for instance, can be followed and recorded by means of its electrical changes.

With each contraction of the isolated muscle a difference of electrical level was established between the two points that were connected with the galvanometer, and an electrical current passed from point of higher level to point of lower level in the muscle, and from point of lower level to point of higher level through the galvanometer, causing the deflection you witnessed.

With an isolated beating heart in the place of the muscle, the same thing would occur at each contraction. A difference of electrical level—a rather complicated difference in this case, by reason of the complication of cardiac muscle—is established between two given points of the heart, chosen, let us say, as far apart as possible near the base and near the apex, and at each beat the

galvanometer index is deflected, or the column of mercury moves, if, instead of a galvanometer, we make use of a capillary electrometer.

The conductors of current in contact with the muscle —or with the heart—are bits of lampwick moistened with normal saline. The tissues of the body have about the same electrical conductivity as that of normal saline. My heart, surrounded though it is by lungs and diaphragm and chest-wall, may after all be considered as being in closer electrical connection with my arms by its upper aspect, and with my legs by its lower aspect. In fact, for the purpose in view you may take an arm and

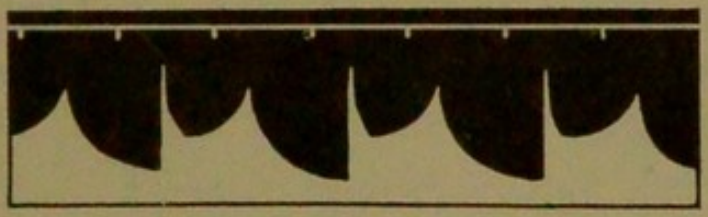


FIG. 2.—Electrometer record of a frog's heart.

a leg as being electrical conductors connected with two different parts of the heart, just as the lampwicks served as electrical conductors connected with two different parts of the muscle. You may regard one arm—say the right arm, since the heart is tilted to the left—as the lampwick in connection with the base of the heart; and one leg—say the left—as the other lampwick connected with the apex of the heart. So that to complete an effective circuit between one's heart and a galvanometer, all that is necessary to do is to dip the right hand and left foot into a couple of pots or pans containing salt-solution from which wires lead off to the two ends of the galvanometer.

I did this some twenty years ago, and I remember, as if of yesterday, the keen pleasure with which I first witnessed the electrical pulsations of my own heart. The

galvanometer—or rather the electrometer—for no galvanometer suited to my purpose was then in existence—was connected with a foot-bath half full of salt-solution in which both feet were plunged, and with a silver electrode in the mouth ; I thought that this would be the best way of getting at the base and apex of the heart. In effect the electrical pulsations made visible in this way were unmistakably distinct.

Then I tried all sorts of connections—with the front and back of the chest, and the mouth and the various limbs. One fact puzzled me exceedingly, and for quite a long time ; with a silver electrode in my mouth connected with one pole of the electrometer, the other pole of which was connected with a basin of salt-solution, I dipped first the left hand then the right hand into the saline, and saw with the left hand in the basin very distinct pulsation, but with the right hand little or no pulsation. The mouth and the left hand formed a good combine, the mouth and the right hand a bad one.[1]

For a long time I was puzzled by the difference, although of course I guessed it was owing to the tilt of the heart. Then I observed that the right hand, which made a bad combine with the mouth, made a good combine with either foot ; and that a foot, making a good combine with the right hand, made a very poor combine with the left hand. Then the puzzle was cleared up, and each bit of it fell into its proper place. By reason of the tilt of the heart, a line AB, between apex and base, which may be taken as representing the axis of the current arising in the heart between its apex and its base,

[1] "On the Electromotive Changes connected with the Beat of the Mammalian Heart, and of the Human Heart in particular." *Phil. Trans. R. S.*, p. 169, 1889. The first electrocardiogram of the human subject was given in this paper ; it is reproduced in the Appendix to these lectures (Fig. 54 ; note 2).

is oblique to the left, and the equatorial line OO at right angles to AB divides the body into two unequal parts—a lesser part *bb* that includes the head and the right

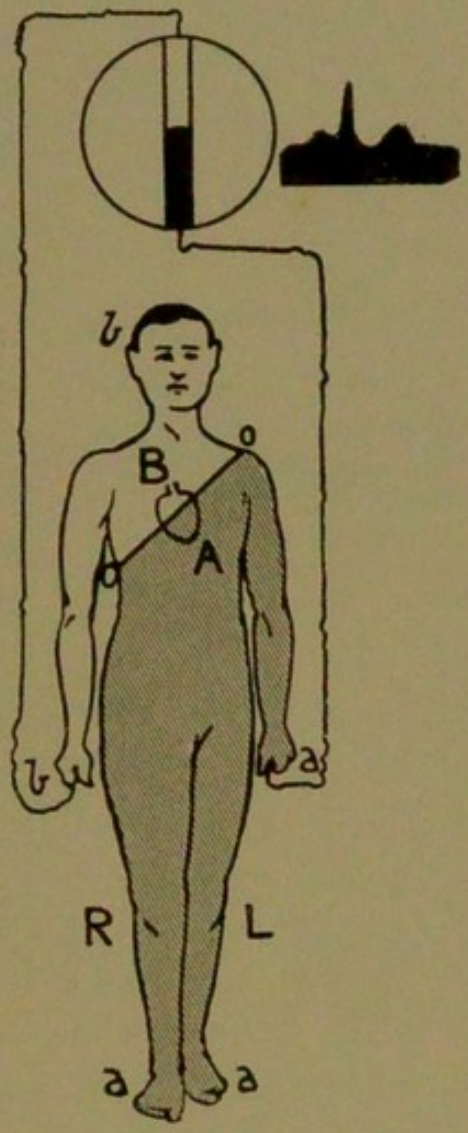


FIG. 3.—Distribution of electrical potential in the human body from Apex and Base of the heart during contraction. The two hands are represented as connected with the mercury and sulphuric acid ends of a capillary electrometer. The alterations of level of mercury with a contraction of the heart are represented at the side of the disc; the latter represents the electrometer as seen in the field of the microscope.

arm, and a larger part *aaa* that includes the left arm and both legs. If we connect with two points *a* and *b* on opposite sides of the equator OO, we have a condition favourable to the manifestation of any difference of

potential between A and B during the beat of the heart. If we connect with two points *aa* or *bb* the conditions are unfavourable.

Accordingly—

The mouth and the left hand form a good combine.
The mouth and the right hand form a bad combine.
The left hand and the right hand form a good combine.
The left hand and either foot form a bad combine.
The right hand and either foot form a good combine.

As soon as I had realized that this was the state of things in normal men I set to work to capture one of those rare cases of *situs inversus viscerum* in which all the organs of the body are disposed as if viewed in a mirror, the heart in particular being tilted to the right instead of to the left. I found two such cases. In these people, as I had expected,

The mouth and the left hand formed a bad combine.
The mouth and the right hand formed a good combine.
The left hand and the right hand formed a good combine.
The left hand and either foot formed a good combine.
The right hand and either foot formed a bad combine.

Everything was correct, including the fact that when the two hands of either of these people were connected with my instrument, there was good pulsation visible as in the case of normal persons, only the direction of the pulsation was reversed. But I have not yet considered the question of direction.

The direction of the electrical pulsation is a rather complicated matter, and so is its interpretation. We had therefore better adopt at once as a convention a uniform plan of connections such that whenever B, the base, is more contracted—or more contract*ing*—than A, there is

movement upwards of our indicator, giving on the record an upward or positive movement. That being settled, we shall have as the indication of the contraction of A, the apex, a downward movement or an interruption of the upward movement due to the action of B.

Here is an electrometer record of the human heart taken by Professor Einthoven, that I have chosen for the sake of showing the close similarity between it and that of the frog's heart.

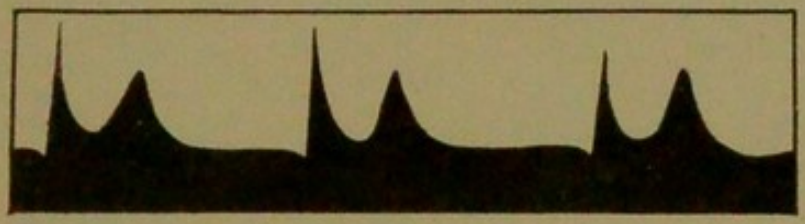


FIG. 4.—Electrometer record of the human heart (Einthoven).

Here is another electrocardiogram (Fig. 5), also taken by Professor Einthoven,[1] who has studied this subject very closely and successfully by means of an instrument of extreme sensitiveness invented by himself—the "Saiten Galvanometer"—that affords indications far more searching and accurate than those that can be obtained with the capillary electrometer. The connections between subject and apparatus are in accordance with the convention just specified. You distinguish upon the electrocardiogram three positive waves, P, R, T. The first of these three is due to the auricular contraction. The second and third belong to the ventricular contraction. (The correspondence between these electrical events and the mechanical movements of the heart indicated by an ordinary cardiograph is shown by the lower line of the figure.) The two elevations, R, T (or B, B),

[1] Einthoven, *Pflüger's Archiv*, vol. 60, p. 101, 1895; vol. 99, p. 472, 1903; and vol. 122, p. 517, 1908.

signify action of the base unbalanced by action of the apex. The intervening valley (A) corresponds to the middle part of the systole during which the entire mass of the ventricles is in a state of contraction.

The simplest view to take of the causation of these features is to consider that a peristaltic wave of contraction sweeps rapidly through the cardiac muscle from venous to arterial end. This can actually be seen to occur in the simple slowly-beating heart of molluscs. But in the

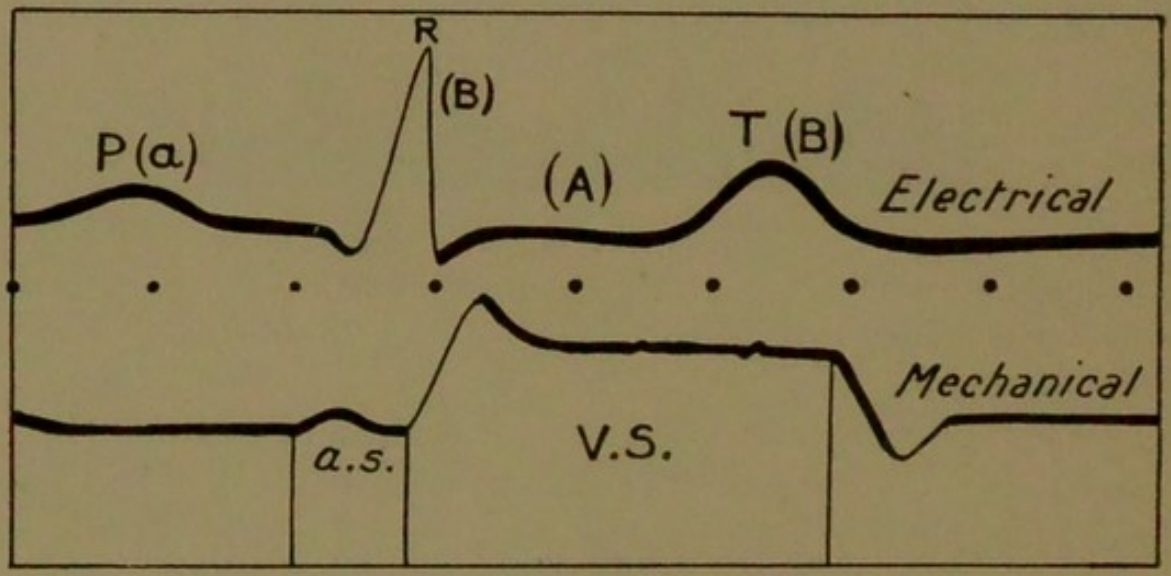


FIG. 5.—A diagram to show the correspondence between the electrical change and the mechanical movement in a contraction of the human heart. *a.s.* represents the auricular systole, V.S. the ventricular systole.

mammalian heart, in which the vascular tube has become looped and twisted upon itself, it is practically impossible to follow out a mechanical wave of contraction ; moreover, the system of fibres—His's bundle—distributed throughout the ventricles from the *septum ventriculorum*, is a further complication. Nevertheless, and in spite of complications, I think we must provisionally adopt the simple view that as regards the ventricles, the sequence BAB, shown on the electrocardiograms of man and of the frog, and—I may add—of the dog, signifies that the contraction,

starting from the auricles, (1) begins at the base, (2) extends to the whole mass, and (3) ends at the base. A ventricular contraction of this character may be regarded as particularly well adapted to the final and complete emptying of the ventricular cavities. Indeed, in the frog we have a ventricular contraction visibly ending in a distinct contraction of the *bulbus arteriosus*.

From observations on man one is naturally led to make similar observations on animals. I have accordingly examined in this way dogs, cats, rabbits, and horses, connecting their feet two by two with the two ends of a suitable gal-

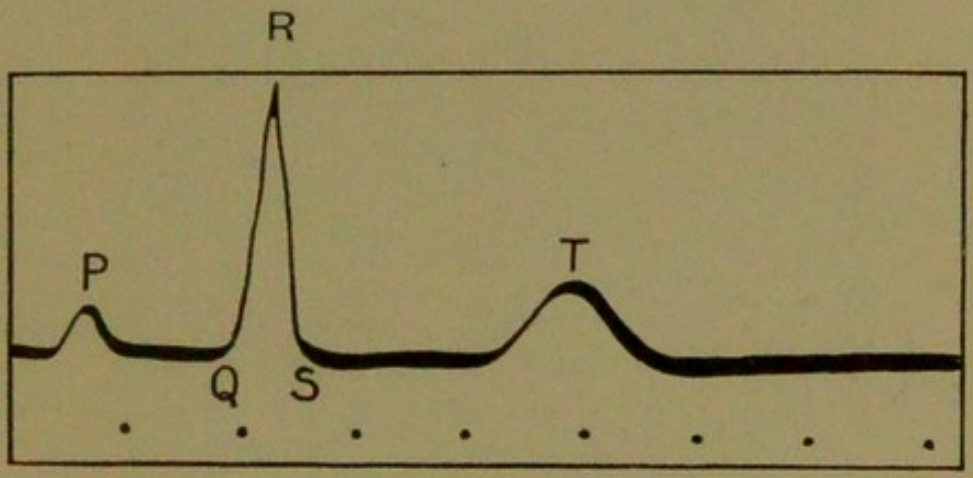


FIG. 6.—Electrocardiogram of the dog, taken by Einthoven's galvanometer.

vanometer or of an electrometer. The results were similar to those observed on man, with some minor differences of detail attributable to the more symmetrical position of the hearts of these quadrupeds. Thus in the dog the difference between the right and left fore-foot is not nearly so pronounced as is the difference in man between the right and left hands.

I should like to say something more about the dog—my favourite animal in this, and in other connections; and I shall scarcely resist the temptation of saying something about a particular dog, by name "Jimmie." The electrocardiogram of a dog is precisely similar to that of

a man, although if one watches the pulsations one notices at once that they are irregular. But that is not an electrical peculiarity, it is a normal feature of the canine heart. All the *canidæ*—not only dogs, but also foxes and wolves (I have not myself felt the pulse of these animals, but I know a man who has)—present this feature of irregularity, which is due to an action of the vagus nerve. Each beat, however, is a perfectly normal beat; you could distinguish the electrocardiac effects of the dog from

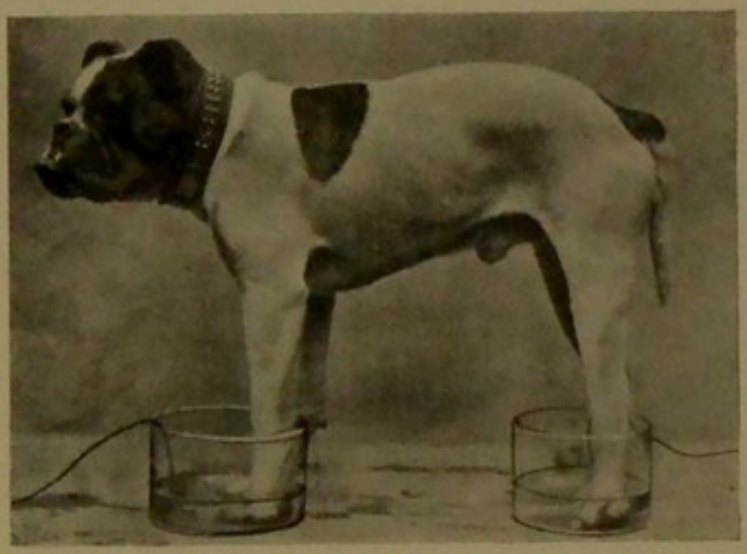


FIG. 7.—"Jimmie" in a state of voluntary immobility, with a front leg and a back leg each in a glass vessel of normal saline connected by wires with the two poles of an electrometer or a galvanometer.

those of man by their irregularity, but not by the record of an individual beat.

A few weeks ago, in London, England, at the Royal Society, I gave a demonstration of the electrical effects of the heart of man and of the dog. For this purpose the man had to keep his hands quiet in a couple of jars of normal saline connected with a galvanometer; the dog had to stand quietly with a front leg and a back leg in the same innocent fluid. My dog "Jimmie," being of a patient breed, and acquainted with the game, as well as

with the satisfaction to his own tastes in which it usually resulted, was used for the purpose. The electrical effects of his heart-beats were projected on a screen, and their irregularity—a feature which, as just mentioned, is characteristic of all the *canidæ*—aroused the commiseration of many persons who witnessed the demonstration. They thought that "Jimmie" was suffering from a bad attack of palpitation of the heart—"allorhythmia" some one called

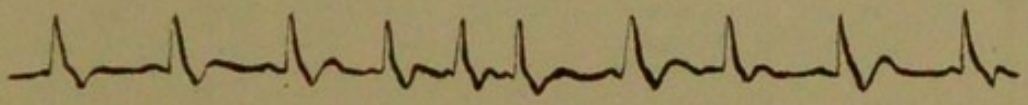


FIG. 8.—Electrocardiogram of a normal dog ("Jimmie"). The irregularity of the heart-beat is normal.

it who was acquainted with recent medical literature. But the story did not end there, and in case any one should feel sceptical as to the literal accuracy of a transatlantic tale, I will finish it by a quotation from the parliamentary report of the *Times* newspaper of July 9, 1909.

"EXPERIMENTS ON DOGS.

"Mr. Ellis Griffith (Anglesey, Min.) asked the Secretary of State for the Home Department whether his attention had been called to a public experiment performed by Dr. Waller on a bulldog at the *conversazione* of the Royal Society at Burlington House, on May 12 last, whereby a leather strap with sharp nails was secured around the dog's neck, his feet being immersed in glass jars containing salts in solution, and the jars being connected by wires with galvanometers: whether, in view of Section 6 of the Cruelty to Animals Act, 1876, which prohibited any exhibition to the general public of experiments on living animals calculated to give pain, he would say whether a licence had been granted to Dr. Waller for the performance of this experiment; whether Burlington House had been registered by the licensee for this purpose under Section 7 of the Cruelty to Animals Act, 1876; and whether any action had been or was being taken in reference to the matter.

"Mr. Gladstone.—Yes, sir; and I have made inquiries. Dr. Waller held no licence for this demonstration, and Burlington House is not registered under Section 7 of the Cruelty to Animals Act, 1876. I understand the dog stood for some time in water, to which sodium chloride had been added, or, in other words, a little common salt. If my hon. friend has ever paddled in the sea he will understand the sensation. (Laughter.) The dog—a finely-developed bulldog—was neither tied nor muzzled. He wore a leather collar ornamented with brass studs. Had the experiment been painful the pain no doubt would have been immediately felt by those nearest the dog. (Laughter.) There was no sign of this, and I do not propose to take any action. (Hear, hear.)

"Mr. Ellis Griffith.—After this exhibition of humour on the part of the right hon. gentleman (hear, hear), may I ask what is the source of his information that no pain was inflicted on the dog? (Hear, hear.)

"Mr. Gladstone.—I have seen Dr. Waller and made the acquaintance of the dog, who is well accustomed to these exhibitions and likes standing in the water. (Laughter.)

"Mr. MacNeill (Donegal, S., Nat.).—With a little salt.

"Mr. Kennedy (Cavan, W., Nat.).—Can the right hon. gentleman say what was the purpose of this exhibition?

"Mr. Gladstone.—To show the pulsation of blood and other functions of the body. It was absolutely painless.

"Mr. Kennedy.—Has the right hon. gentleman received an assurance that the dog was not drugged for the experiment?

"Mr. Gladstone.—There is no question of the dog being drugged. It was a perfectly harmless demonstration, which might be carried on at any place without the slightest pain to the dog, and to the edification of the spectators.

"Mr. MacNeill.—Will the right hon. gentleman inform the person who furnished him with his jokes that there are members in this House who regard these experiments on dogs with abhorrence? (Hear.)

"Mr. Gladstone.—I certainly shall not. The jokes, poor as they are, are mine own. (Laughter and cheers.)"

This is the *Times* report.

The astounding and lamentable truth is that men and women—for lack of a little understanding and a little goodness—should be so ready to impute evil in defiance of all common sense. What indeed can be the humour

of mind that permits a man to picture as a rational act of cruelty the exhibition of a dog at the Royal Society "with a leather strap with sharp nails secured around the dog's neck"?

It would be a sufficient justification for the telling of this tale if it might cause any one of the good people who have suffered their minds to harbour infamous thoughts, to call in question the all-sufficiency of their own intelligence and the morality of their endeavour to poison the wells of human sympathy against they know not what.

But do not mistake me. I am opposed to the anti-vivisecting crusader. I do not think fit to justify vivisection in the mind of the man in the street or of the lady in the drawing-room. I am willing to justify the practice of vivisection to the competent and educated man only; but I think he knows already that our rights to vivisection are not lightly claimed nor lightly exercised.

To review our hour's work. What have we got to show for it? Not much, perhaps; certainly no great discovery; little more than a somewhat clearer knowledge of what we knew already—that by very simple methods we can get new knowledge and may hope for more; and that the electrical action of a man's heart can be studied without cutting him open. And perhaps we may have learned from the dog story to distrust our own judgment as well as that of other people.

LECTURE II

We have seen that the contraction of muscle—cardiac muscle as well as ordinary muscle—involves electrical changes that can be observed and recorded. We shall turn our attention now to tissues in which electrical changes are practically the only means of observation—namely, nerve and skin and retina. We may of course learn a good deal about nerve by means of its natural indicator—the muscle to which it is distributed. But in many respects the information about nerve so obtained is liable to be ambiguous. We can, for instance, study the fatigue of muscle by repeated direct excitation of the muscle itself, but the attempt to study the fatigue of nerve in the same way by means of its muscle fails us, because the effects observed can be—and, in fact, are—due to the muscle itself, or to the junction between nerve and muscle—and not at all to the nerve.

In order to be quite sure that we are dealing with nerve, and nothing else but nerve, we must get rid of muscle, and have nothing but the nerve in connection with our instruments. So a nerve—the sciatic nerve of a frog in 99 cases out of 100—is cut out and laid across two pairs of electrodes; one pair to put the question, the other pair to take the answer. And now you are quite sure that any alteration of response is really due to an alteration of the nerve and of nothing else. Of course I am using the word "nerve" in its strict anatomical

sense, and not in a loose way to include nerve-terminals as well as nerve-fibres.

We put our questions to the nerve, "Are you alive?" "How much are you alive?" through one pair of electrodes, and we get a clear answer "yes" or "no" or "so much" through the other pair of electrodes at a distance from the first pair, and in that case we test the conductivity, or indirect excitability, as well as the direct excitability of the nerve. We can, if necessary, put the question and receive the answer through the same pair of electrodes, in which case of course we should be testing only the direct excitability.

Skin can be treated in very nearly the same manner. A piece of skin of a frog, or of man, is fixed up between one pair of electrodes through which it will receive the question and deliver the answer. Or we may test the indirect excitability of the skin by stimulating its nerve. Each of the two plans has its advantages and its limitations according to the kind of information we want to obtain.

If now I went on to show you the recorded result of a preliminary experiment on an isolated nerve, I think you might be tempted to regard it as a very mechanical result —physical rather than physiological; the regularity of the nerve-response is really too perfect; it is too good to be true; and I should have to hasten to show experiments with an anæsthetic, or with some drug having a special action upon the nerve, to make you feel that we are really dealing with changes peculiar to *living* nerve. Your dissatisfied state of mind would indeed have been very justifiable; it has been—and still is—shared by not a few physiologists, who fight shy of the difficulties and pitfalls that are associated with electrical methods.

So I am anxious to take the earliest opportunity of showing you an experiment that, in my judgment, is

beyond all comparison the best and the most convincing experiment in electrophysiology.

It is an experiment on the skin, excited through its nerve. The experiment is not complicated. A galvanometer is in connection with two electrodes touching the skin of the two hind legs of a cat that was decapitated about half-an-hour ago, and the sciatic nerve of one side is laid across another pair of electrodes through which it can be stimulated at will by tapping a key in the primary circuit of an induction coil. The sciatic nerve contains, as you know, several sorts of nerve-fibres, that conduct stimuli to muscle, causing contraction, and to subcutaneous glands, causing secretion. And there are other sorts of fibres that do not at present concern us. We are, in fact, very little concerned with the muscular nerve-fibres, and it will simplify matters if we wait till the dying tissues are dead enough for stimulation of the nerve to give no more muscular contraction. For when there is no more contraction there is no more electrical effect from the muscle, and the electrical effect that we shall witness will be due to some tissue other than muscle—namely to the skin.

The best animal, and the best time after death for the experiment, is a cat during the second and sometimes the third half-hour after decapitation ; we then shall find the still living tissues of the dead animal in the most suitable state, *i. e.* the muscles inexcitable from the nerve, the glands still excitable. When the nerve is stimulated by a single induction shock there is, as you see, an unmistakably sharp and sudden deflection, the features of which are well worth your attention.

Take notice, in the first place, that quite a long time elapses between the tap of the key and the excursion of the galvanometer spot. I tap, and have time to think whether the spot intends to move or not, before it

actually moves ; and then it moves with a sharpness and decision that are altogether satisfactory. The latent period —and it is a true latent period in spite of its great length —is something like two seconds ; you can measure it by stop-watch if you choose. Clearly there can be no question of current-diffusion from the stimulating to the galvanometer circuit, for current-diffusion does not wait two seconds ; it takes place at once if it takes place at all.

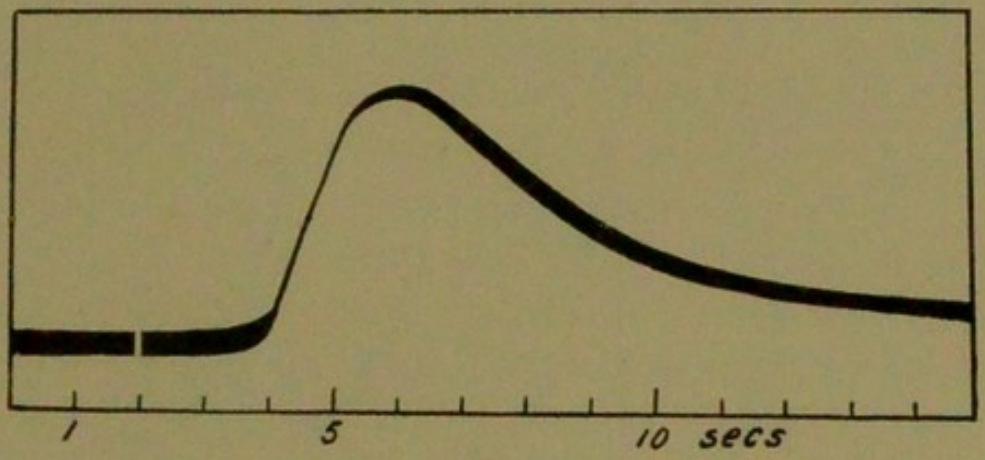


FIG. 9.—Electrical response of the pad of a cat's foot to a single induction shock applied to the sciatic nerve forty minutes post mortem. The latent period is 1·5 seconds. It is indicated by the vertical white mark.

The effect is due to a chemical action—to the cell-metabolism taking place in the glands of the cat's foot, that results in the production (and secretion) of the organic constituents of sweat. It occurs, however, in the absence of any visible secretion, and is therefore attributable to the preparatory chemical change, rather than to any outflow of liquid.

Does not the deflection of that spot of light acquire new value in your eyes, when you have realised that it is beyond all doubt the sign and measure of the otherwise invisible activity of living cells provoked by the equally invisible activity of living nerve-fibres ? And in this connection, if it occurs to any one to ask what is the effect of atropine upon it, I may say at once that the

deflection does not occur on an atropinised cat ; whereas it always occurs on a normal cat—at least, I have not yet known it to fail. And it invariably takes place in one direction—always so that the current goes in the body from excited to unexcited side, that is to say from without inwards, or "ingoing" through the excited skin, *i.e.* against the direction of secretion.

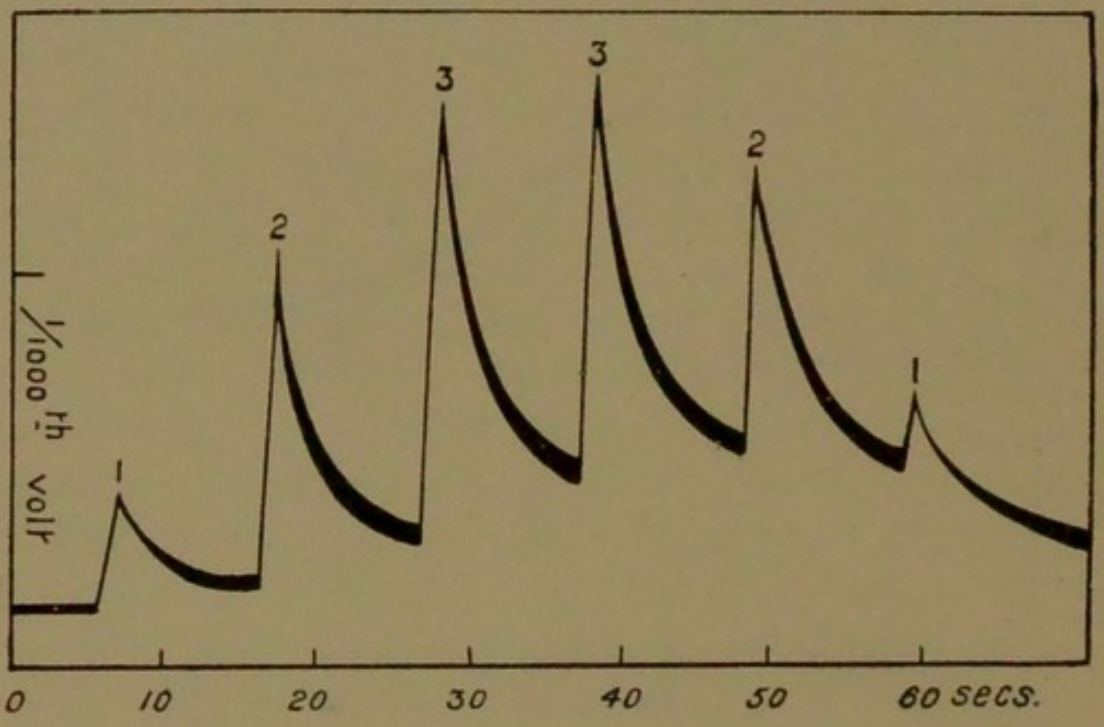


FIG. 10.—Indirect electrical responses of cat's skin by 1, 2, 3, 3, 2, 1 shocks to the sciatic nerve.

I used a single induction shock just now, and rather a strong one, in order to make sure. If now I take a weaker shock, first finding by trial a strength that will give a moderately small deflection, I shall be able to demonstrate with much more certainty and accuracy than I could in any other way or on any other tissue (1) summation of stimuli, (2) the relation between magnitude of stimulus and magnitude of effect.

Taking, at this moderately low strength, the effects of

one, two, three, and more stimuli, you see an increasing scale of effects up to some maximal value.

Taking, beginning at this moderately low strength, the effects of stimuli of twice, three and more times that strength, you see again an increasing scale of effects up to a maximal value.

But I do not wish to dwell on details more than may be sufficient to convince you that the experiment gives the clearest possible proof that an electrical change is the sign and measure of a physiological change. For further details you may consult two papers published some time ago in the *Proceedings of the Royal Society*.[1] The fact itself was discovered many years ago by B. Luchsinger ;[2] the only credit to which I can lay claim in connection with it is to have put it into a very simple form on a recently-killed animal, so that it is very easy to repeat with unmistakable and convincing results, and without involving a vivisection.

Let us now return to the isolated nerve—taking as before a frog's sciatic. We know that when the nerve is stimulated something happens ; an impulse has been aroused by the stimulus, has traversed the nerve, and has set in motion a muscle or a gland or a nerve-centre.

We want to know about that impulse. It is a wave of change transmitted in both directions along the fibres of extremely labile stuff of which the essential part of the fibre consists. Shall we reckon the change as "physical" or "chemical"? It may not matter very much which we

[1] Waller, "On Skin Currents," Part II. Observations on Cats, *Proc. R. S.*, vol. 69, p. 173, 1901. "The Secreto-motor Effects in the Cat's Foot, studied by the Electrometer," *Ibid.*, vol. 73, p. 92. See also *Lectures on the Signs of Life*, 1903, p. 97 (Murray, London).

[2] Hermann v. Luchsinger, "Ueber die Secretionsströme der Haut bei der Katzen," *Pflüger's Archiv*, xvii., p. 310, 1878.

call it ; indeed, in these days of Physical Chemistry, it is difficult to draw any sharp line of demarcation between physical and chemical change ; yet, all things considered, we shall prefer to regard the nervous impulse as being a chemical change, extremely brief and perfectly reversible. And refraining from any discussion concerning the electrical mechanism of chemical change, admitting indeed that the words " electricity " and " chemical affinity " apply to one and the same force, we shall pursue matters from the simple standpoint taken up in Lecture I, to the effect that the chemical changes taking place in living nerve are signified and measured by electrical changes.

The only sign we can have that an isolated nerve is alive, traversed by impulses, is furnished by electrical instruments—by a galvanometer or by an electrometer. It was, in fact, because in this case the electrical indications stand alone, without any possible control or support by any other kind of testimony, that I laid stress upon the parallelism between mechanical and electrical indications in the case of muscle, and was at some pains to establish in your mind, by the experiment on the cat's foot, the high degree of credit attaching to the sign.

It is not an easy task to get the graphic record of a single nervous impulse ; it is much less difficult, and for many purposes preferable, to work with the sum of many such impulses obtained by a brief period of tetanisation. Thus in Fig. 11 each of the two successive deflections is the effect of a tetanisation lasting for $7\frac{1}{2}$ seconds at an interruption frequency of 50 per second, *i. e.* of a group containing 375 separate impulses.

Considering each of these deflections a little more closely, we note that it consists of a negative deflection during the tetanisation, followed by a positive after deflection.

The negative deflection (du Bois-Reymond's negative variation) is the summated effect of the series of brief negative impulses aroused during the $7\frac{1}{2}$ seconds' tetanisation. The positive after-deflection (Hering's positive after-variation) is the continuous effect of a continuous state of nerve subsequent to the period of tetanisation. Do not suppose that this after-deflection is an instru-

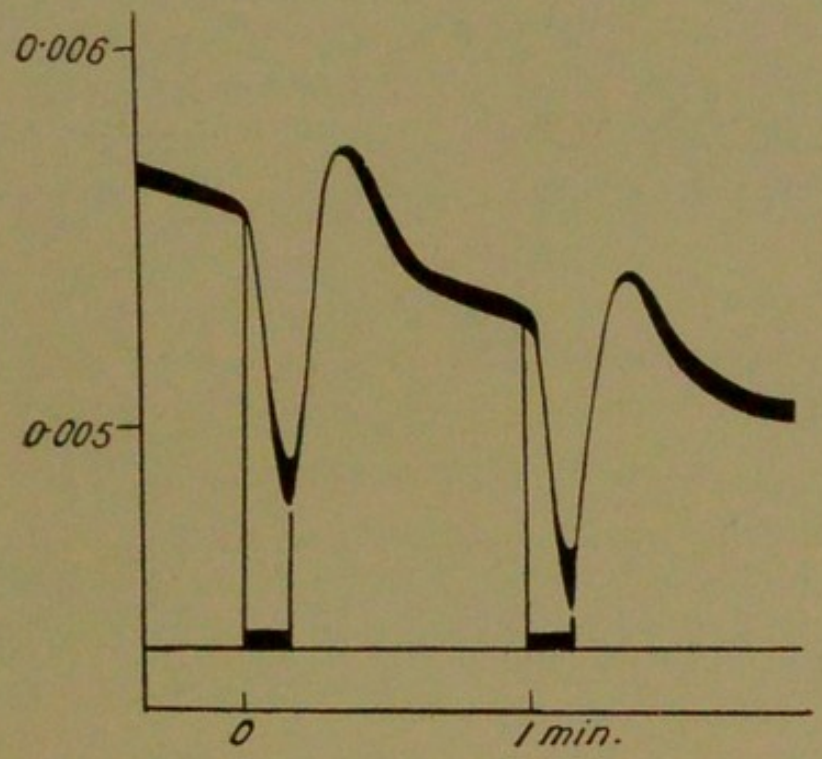


FIG. 11.—Two normal electrical responses to 7·5 seconds' tetanisation of an isolated nerve. Each response consists of a negative deflection during excitation, followed by a positive after-deflection at the end of excitation.

mental over-swing. The galvanometer is dead-beat, and the over-swing—so to call it—is an over-swing of chemical state; the nerve recovers, and more than recovers, the state it was in before the tetanisation.

We shall discuss the possible significance of these two deflections later. At present, and apart from any theory, we shall find it profitable to examine the modifications of these two main features brought about by experimental means.

But before doing so there is one other principal consideration that should be clearly before our minds, if we are to come to any good understanding of what we are about to see.

If I cut a nerve and lay it across the galvanometer electrodes, as I am now doing, with the cut end on one electrode and an intact part on the other, you will see a large steady deflection which very gradually subsides. That deflection is due to a current of injury (Hermann's current); the cut end of the nerve is in a state of continuous excitation; it is at a higher electrical level than other parts of the nerve. So that in the nerve there is a

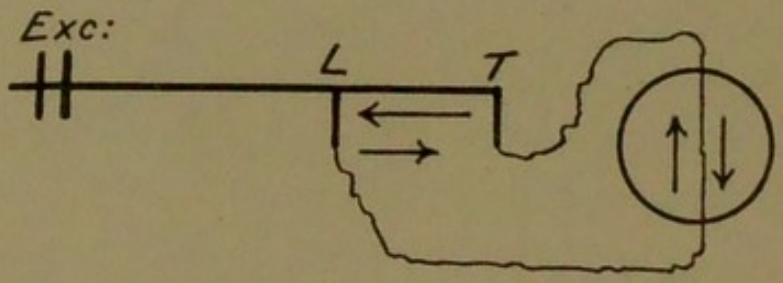


FIG. 12.—Diagram of an isolated nerve laid across exciting electrodes EXC., and leading off electrodes L and T connected with a galvanometer. As indicated by the arrows, the current of injury in the nerve is from T to L, and the normal negative response to excitation is from L to T.

current from the point T to the point L, completed through the galvanometer in the direction L to T, *i. e.* upwards in the figure. And the negative variation is in the opposite direction, from L to T and downwards through the galvanometer. The impulses transmitted along the nerve arouse action and rise of electrical potential at L, but not at T where it is already raised by injury.

This is a photographic record showing a series of negative variations followed by their positive after-effects, at one minute intervals, in the course of a gradually declining current of injury. We may take it for thinking purposes that the negative variation signifies chemical

disintegration and that the positive after-variation signifies chemical reintegration (Fig. 13).

The first thing to do in order to learn whether a regular effect like this is physiological or not, is to test it by an anæsthetic. If under the influence of ether vapour, for instance, it disappears, and if after removal of the vapour it reappears, we may be quite sure that it is not merely physical, but physiological as well—a true sign of life.

There can be, as you see, no doubt whatever as to the

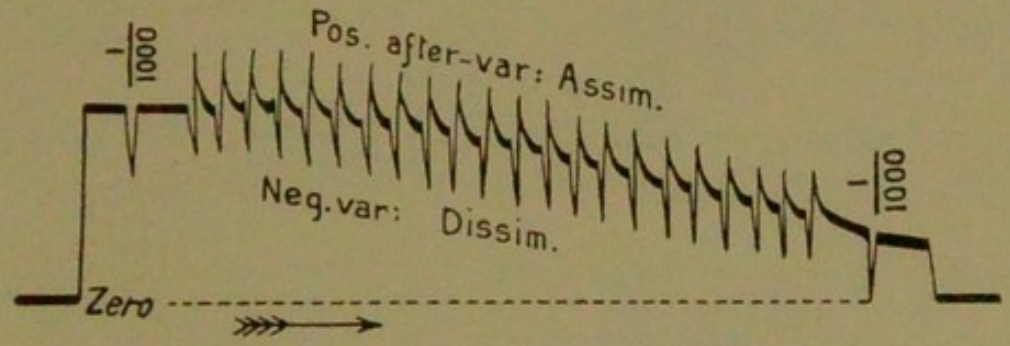


FIG. 13.—A series of normal responses of an isolated nerve, each consisting of a negative deflection followed by a positive after-deflection. The former is considered to be significant of "dissimilation," the latter of "assimilation." The single deflection at beginning and end of the series is a standard deflection by $\frac{1}{1000}$ volt. The current of injury is gradually declining.

result of the trial. Clearly the negative deflection on our records is a sign of life of the nerve, and one that can obviously be utilised for all kinds of exact trials in connection with the power of various reagents. Our test-object, an isolated nerve, does not move when it is excited, and does not sensibly alter, either spontaneously or in consequence of excitation many times repeated. Any alteration taking place after the nerve has been interfered with can be safely attributed to the interference, and if no alteration has taken place we may safely conclude that the interference was ineffective. We shall not be worried with doubtful results.

When one has witnessed the effect of ether, he naturally goes on to try chloroform. I did so, of course, and at first without paying any special attention to the percentage of chloroform to which the nerve was submitted. The variations were abolished, as in the case of the etherised nerve, but they were *permanently* abolished ; the nerve never recovered its excitability, it had been killed by chloroform.

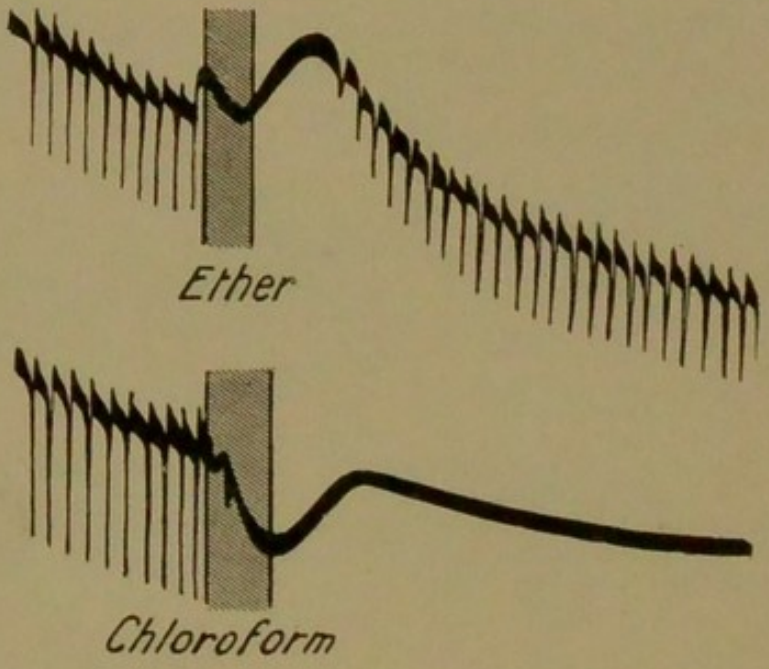


FIG. 14.—Influence of ether and of chloroform vapours of considerable concentration upon the normal electrical responses of isolated nerve. The shaded vertical bars indicate the time during which the vapour was allowed to act. Excitations were applied at 1 minute intervals throughout both records. Recovery after complete anæsthesia began in the case of ether in about 5 minutes. No recovery took place in the case of chloroform.

This experiment, which I first made some fifteen years ago, has caused me much thought. It seemed to me to represent, as in a nutshell, anæsthesia of the human subject. It was a rough-and-ready experiment representing in the laboratory the sort of thing that can happen in rough-and-ready practice, when the vapour of ether or of chloroform is used—carefully, perhaps—but with very

indefinite knowledge of their strength or of their quantity absorbed. I then thought it very probable that chloroform accidents ascribed to "idiosyncrasy" might in reality be due to overdose.[1] I thought that we required above all more precise knowledge of power and quantity, and have since then done my best to acquire such knowledge. Yet to-day, although I hear less about idiosyncrasy and more about actual quantity and percentage, I still recognise an excessive disposition to invoke any cause other than simple overdose to account for fatal accidents; deaths that may or may not have been due to excess of chloroform, in which it is absolutely impossible to say that there

[1] The drift and purpose of my contention will be evident from the following list of publications on the subject during the last twelve years—

1. "The Action of Anæsthetics upon Nerve," *British Medical Journal*, Nov. 20, 1897.
2. "The Dosage of Chloroform," *Ibid.*, April 23, 1898.
3. "Reports to the Special Chloroform Committee of the British Medical Association," *Ibid.*, July 12, 1902.
4. "A New Method for rapidly estimating Chloroform Vapour," *Proc. Physiol. Soc.*, July 19, 1902.
5. "On the Physical Relation of Chloroform to Blood," *Proc. Royal Soc.*, vol. 74, p. 55, 1904.
6. "On the Administration of Chloroform to Man and to the Higher Animals," *Lancet*, Nov. 28, 1903.
7. "Chloroform and Ether Estimation by Densimetry," *Proc. Physiol. Soc.*, July 11, 1903.
8. "Estimation of Inspired and Expired Chloroform," *Ibid.*, Feb. 25, 1905.
9. "A Physiological Contribution to the Problem of Chloroform Anæsthesia," *British Medical Journal*, Dec. 24, 1904.
10. "On the Action of Anæsthetics," *British Association, Leicester*, 1907.
11. "The Chloroform Balance; a New Form of Apparatus for the Measured Delivery of Chloroform Vapour," *Proc. Physiol. Soc.*, Feb. 1908.
12. "The Price of Anæsthesia," *Science Progress*, April 1908.
13. "Report on Anæsthetics," *British Association, Winnipeg*, Aug. 1909.

has or has not been excess absorbed, are now attributed to "*status lymphaticus*." [1]

Obviously the first question to be studied in the laboratory, for its own sake, and for the sake of the hospital, is the question of quantity, and that question is of most pressing importance as regards chloroform. How much chloroform is required to produce anæsthesia? How much chloroform is dangerous or assuredly fatal? How shall we best administer the smallest sufficient quantity of chloroform?

These are eminently practical questions that require to be answered by careful experiments in the physiological laboratory, completed by careful observations in the hospital. And so I was led to make experiments on the isolated tissues of animals, and on animals themselves—on isolated nerve, on the spinal cord, on isolated muscle, on the heart, on blood-pressure—that have little by little brought out what to my mind are clear and satisfactory answers, both as regards the smallest sufficient quantity required, and as regards simple methods of determining such quantity, as well as of regulating it during administration.

These experiments have engrossed my attention ever since; I do not propose to consider them further to-day; our attention is centred now upon nerve, not upon anæsthetics, to which, however, I hope to devote at least one of our forthcoming lectures; all I wanted to do at this stage was to indicate how the laboratory and the hospital have business together in ways that you might hardly have anticipated. I for one did not do so when I

[1] In the *British Medical Journal* of January 25, 1909, a case of death during chloroform anæsthesia is reported by a professional anæsthetist under the misleading title, "A fatal case of '*status lymphaticus*.'" And the previous pages of the same issue contain an elaborate argument by another professional anæsthetist to the effect that death during chloroform anæsthesia is so frequently associated with "*status lymphaticus*" that it may be asked whether death under chloroform ever occurs apart from that condition.

first etherised a nerve to see whether its response was physiological or not.

The study of the *action of carbon dioxide* upon isolated nerve is interesting in more ways than one, and deserves that we should spend some time upon it.

The first thing you notice when you give a little carbonic acid to a nerve, set up to respond once a minute, is that the negative deflections grow larger ; if you go on giving carbonic acid freely, they then grow smaller and disappear altogether ; if now you stop the carbonic acid and leave the nerve time to recover in ordinary air, it does so perfectly, and the deflection may even become larger than at the beginning of the experiment. The full action of a sufficient quantity of carbonic acid has been like that of ether, viz. a temporary abolition of excitability.

When I first described these effects thirteen years ago,[1] I said that the first effect of little CO_2 was an augmentation of excitability, but it has since been objected to this form of statement that under the conditions of the observation the augmented deflection is due to the augmented *duration* of the separate impulses summed up in the deflection rather than to their augmented *magnitude*. I freely admit this, and shall therefore—without, however, committing myself to an opinion whether the greater deflection is due to greater duration, or to greater magnitude of impulses, or to both factors—confine myself to the simple statement of fact that the negative deflection is augmented. I must leave you to judge whether or no such augmentation is to be regarded as a sign of augmented excitability ; for my part I think it is ; in the case of other tissues—*e.g.* nerve-centres, and the heart—and in that of green leaves excited by light (p. 86), where there is no question of a sum of effects, the influence of carbonic acid consists in augmented followed by diminished activity.

[1] *Phil. Trans. R. S.*, "Croonian Lecture," 1896.

The positive after-deflection is not a sum of separate impulses, but the result of a continuous state ; it is always diminished or abolished under the influence of carbonic acid.

Sometimes—especially in nerves that have been left in salt solution for a long time after excision—the electrical effect during excitation, instead of being negative, is positive. This positive deflection can be regarded as a sum of positive after-effect of individual negative im-

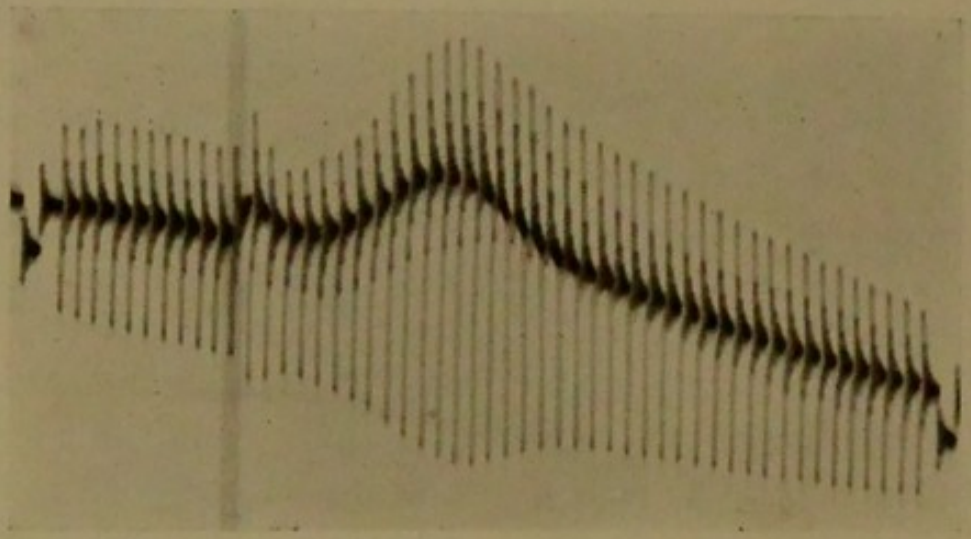


FIG. 15.—Action of little CO_2.

pulses. The ordinary negative deflection is the final resultant of two opposed sums of impulses—negative during and positive after each induction shock. When —as in fact is generally the case—the negative deflection becomes smaller after a long time, this is probably due to the increasing sum of positive after-effects rather than to the diminishing sum of negative effects. Thus analysed it becomes apparent that the negative deflection is a composite effect. We had best therefore take it as we find it, without making any inference from increased and diminished deflection to increased and diminished excitability.

Let us not make any confusion between the negative deflection (and the positive after-deflection) and the individual negative-and-positive impulses of which the negative deflection is composed. Fig. 17 will serve to prevent any such confusion and to make clearer, than otherwise might be, the further development of our argument and description. It will lead us to a better understanding of variations, sometimes encountered, from the normal

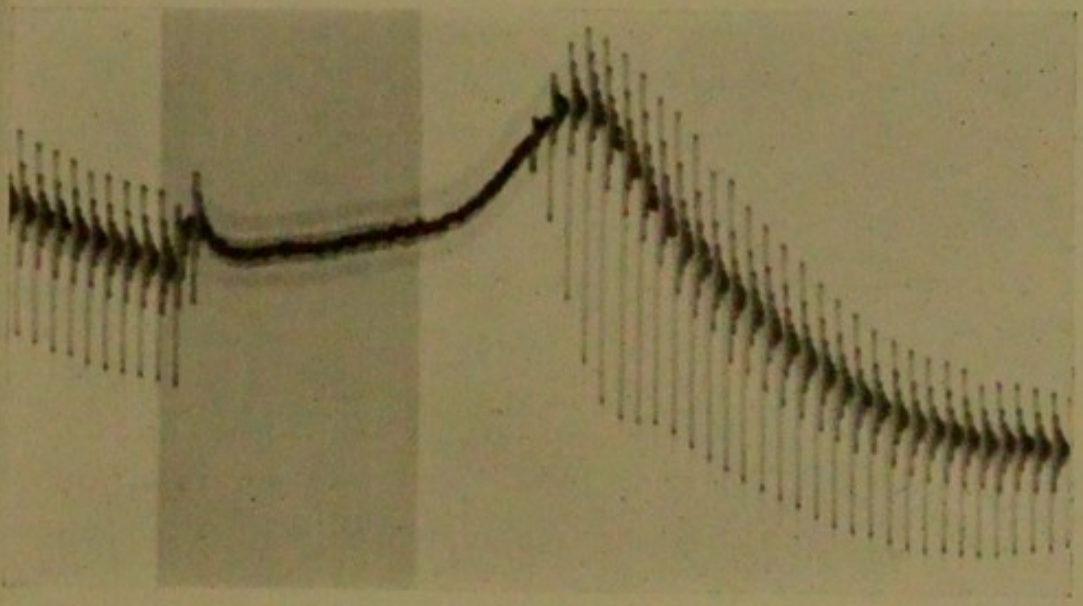


FIG. 16.—Action of much CO_2 (from Waller's *Lectures on Animal Electricity*, 1897, p. 47).

deflection, viz. in place of large negative followed by small positive, we may have small negative followed by large positive, or we may have a prolonged positive. In the first of these cases the positive sum during excitation is considerably smaller than the negative sum, in the third case it is larger, in the second case the positive and negative sums are more nearly equal. We shall distinguish these as deflections of the *first*, *second*, and *third* stages. And we shall refer the visible changes of these visible deflections to similar changes as to their invisible components.

If we give carbonic acid to a nerve exhibiting a deflection of the second stage, we shall find that the positive after-deflection is diminished and the negative deflection increased. We take this as signifying that within the

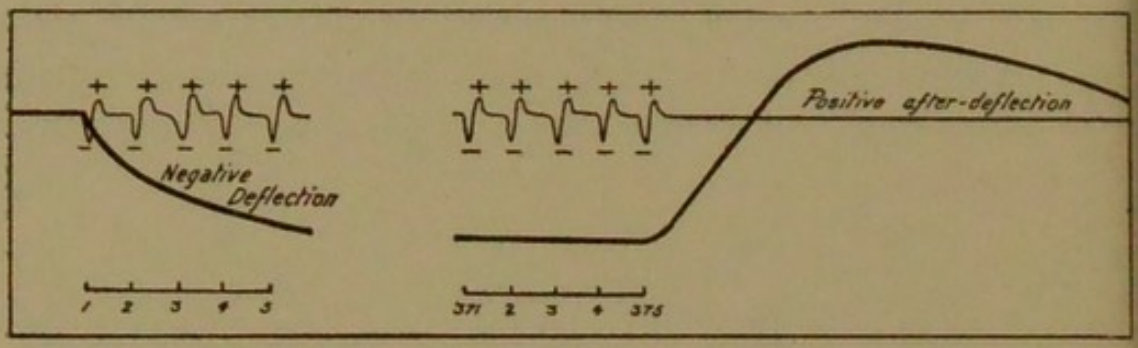


FIG. 17.—Diagram to represent on a greatly extended scale of time the beginning and end of a negative deflection caused by a group of 375 separate − + impulses during 7½ seconds. The impulses are at 50 per sec., so that the time-scale below the figure is in fiftieths of a second.

group the positive sum has been diminished. Finally, if we give carbonic acid to a nerve exhibiting a deflection of the third stage, we shall find that the positive deflection is diminished or actually reversed—a result attributable

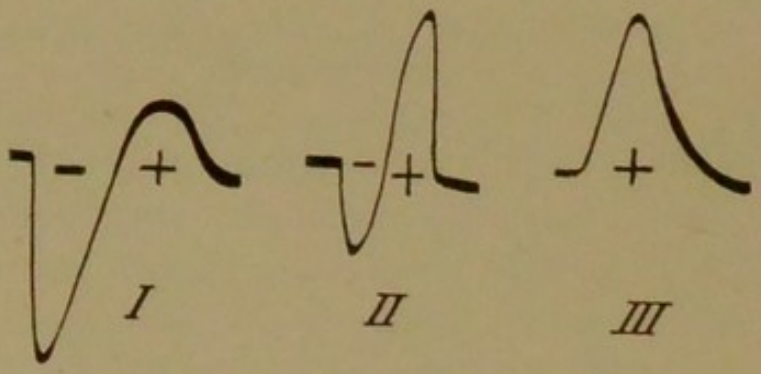


FIG. 18.

as before to a diminution of the positive sum, and an unmasking thereby of the negative sum given by the individual impulses.

Summarising our results, as regards the action of carbonic acid, we have—

1. The negative deflection of the first stage increased, then diminished.

2. The positive after-deflection of the second stage diminished (and the negative deflection increased).

3. The positive deflection of the third stage diminished or reversed. All of which results are to be brought under the one principle that carbonic acid *reduces positive movement or positive change before it disfavours negative movement or negative change.*

We have left as an open question whether or not carbonic acid ever really augments negative change ; we shall, however, be brought back to this question in connection with the action of carbonic acid upon the grey matter of the central nervous system, and upon the green matter of vegetable tissues.

As regards a prolongation of individual negative impulses, which as has been seen can be invoked in explanation of an increased negative deflection, we shall find that this prolongation can itself be accounted for as the result of a disfavoured positive movement. But to make this point clear we shall find it more convenient to reserve it for study in connection with the action of veratrine (p. 46). And I have not done with carbonic acid.

The production of carbonic acid by nerve? One of the first questions calling for trial in connection with nerve, is whether any evidence can be obtained of a chemical alteration of the nerve in consequence of its activity. Considering that no heat-production can be demonstrated, and that hardly any sign of fatigue is manifested, it is not surprising that no chemical change can be detected by ordinary chemical methods ; there is not, as in the case of active muscle, any demonstrable acidification after prolonged tetanisation.

The question of the *fatigue* of nerve deserves some consideration. In the first place, nerve, as compared with muscle, appears to be practically inexhaustible by prolonged tetanisation. An elegant way of bringing out the contrast between nerve and muscle in this respect is—taking advantage of the fact that a nerve stimulated at a given point conducts equally well in both directions from that point—to stimulate the nerve of a nerve-muscle prepara-

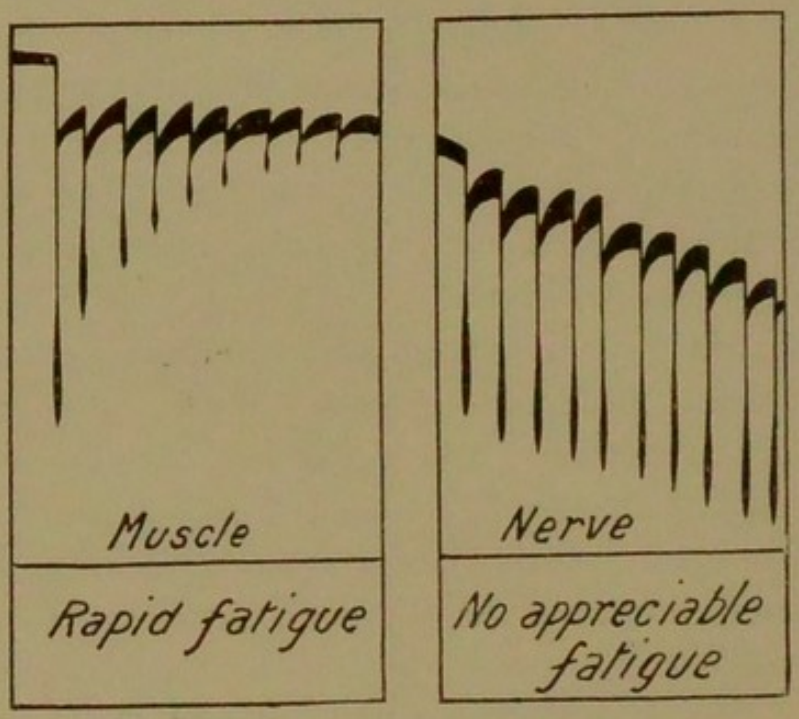


FIG. 19.

tion near the middle of its length, and to make it talk at both ends—at its central end by the galvanometer, at its peripheral end by the muscle. After, say, half-an-hour's work, you learn by the galvanometer that the nerve response proper has undergone no appreciable diminution, whereas the muscle is almost or completely exhausted.

Yet, while this experiment shows quite clearly that muscle is far more easily fatigued and exhausted than nerve, it does not show that nerve suffers no change at all, and we are not entitled to say that nerve is an absolutely unfatiguable tissue. *A priori* it is difficult to admit

such a conclusion. While we may recognise as most natural that nerve—of which the function is simply conduction—should fulfil its function with a minimal expenditure of energy, we should be very loth to accept that there can be a total absence of expenditure. Such a view would seem to make of the nerve a *perpetuum mobile*, expending no energy, or indefinitely restoring expended energy. Considering that nerve has to conduct impulses rapidly and in rapid succession, we may—indeed, must—admit that conduction is effected with a minimal expenditure and with a maximal recuperative power ; but to admit that such action can be kept up indefinitely, without resulting in any chemical change whatever, is not reconcilable with the view that conduction is a chemical function, and is, I think, contradicted by the experiments we are now about to consider.

As to the production of CO_2, we have seen that the first effect of carbonic acid is to augment the negative deflection. A very small amount of carbonic acid is sufficient to produce this augmentation ; breathing once upon a nerve will produce an obvious augmentation. Thus the nerve itself acts as a most delicate indicator of the presence of carbonic acid, as is shown by Fig. 15.

I argued from this fact that if forced action—tetanisation—gave rise to any nerve change at all, of which presumably a production of CO_2 must form part, we should, in consequence of such forced action, witness a similar augmentation of the negative deflection.

This forecast was at once found to be fulfilled by experiment—many times repeated. Tetanisation of moderate strength, kept up for a few minutes, almost certainly brings out the augmentation characteristic of the first effect of carbonic acid.

To bring out the full effect of CO_2, viz. diminution of the negative effect, has in my experience proved to be

more difficult ; indeed, it requires a length and strength of tetanisation that arouse doubt as to the cogency of the result, for it might be a mere injury effect, from which, however, recovery does occur.

Then I submitted to similar forced action by tetanisation, nerves of the second stage, giving, when acted upon by CO_2, abolition of the positive after-deflection (as well as aug-

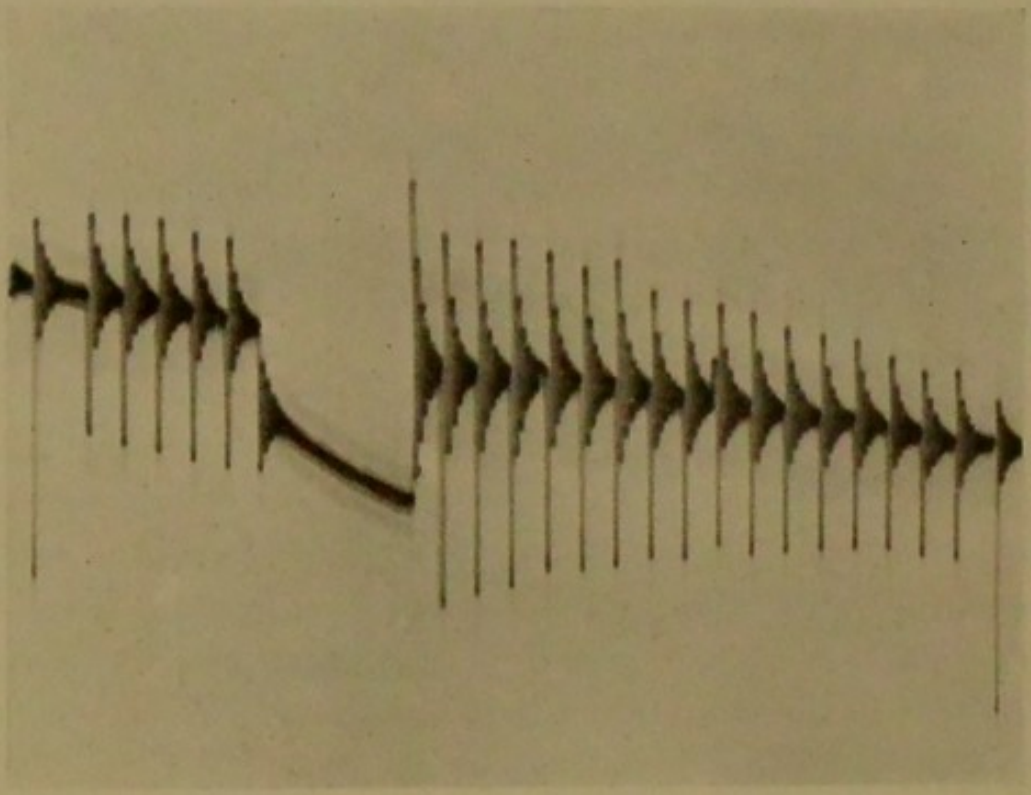


FIG. 20.—Negative deflections of a nerve before and after tetanisation lasting for five minutes.

mentation of the negative deflection). Tetanisation of such nerves gave identical results, viz. diminution of the positive after-deflection and augmentation of the negative deflection.

Finally, I took nerves of the third stage, giving, when acted upon by CO_2, diminution or reversal of the positive deflection. Tetanisation of these nerves gave diminution or reversal of the positive deflection.

Thus the effects of tetanisation were found to be under all conditions and in all points similar to the effects of

CO_2. To my mind the conclusion to be drawn from this identity of effects of tetanisation and of carbonic acid is that the cause in both cases is identical. The evidence that tetanised nerve produces carbonic acid appears to me at least as cogent as the evidence afforded by any conventional chemical test.

If, nevertheless, any one still objects to this conclusion that I have not extracted and identified by objective chemical tests this unseen carbonic acid, I should say: "Granted, and I have never thought of trying to extract carbonic acid from tetanised nerve. I prefer the delicate test by galvanometer to any chemical test for CO_2, even if the latter were possible, and in spite of the fact that the nerve-test is a new test. If, after all, you think it is not carbonic acid but 'something else' that produces effects like those of carbonic acid, I am quite satisfied."

We have throughout had under our consideration *medullated* nerve-fibres, which are essentially the immensely elongated processes of nerve-cells (axons), surrounded by sheaths of white matter. I am disposed to attribute the extraordinary endurance and "restorability" of nerve to this feature, which lends itself to the exchange of ions between axis and sheath. And I regard the white matter of which the sheath is composed as forming a practically inexhaustible store from which the grey axes of an isolated nerve are enabled to remain physiologically active with such remarkable persistence. Proof of the existence of a close nutritional relationship between axis and sheath is afforded by the facts of Wallerian degeneration; alterations of structure then take place not only of the axis itself, but also and most prominently so in the surrounding sheath, which is not in any organic continuity with the trophic cell of the nerve-fibre, but only in some indirect chemical relation with it through the intermediation of the axis. Confirmation of this point of view was obtained by Miss

Sowton,[1] who found that the olfactory nerve of the pike, composed of grey fibres without medullary sheath, is exhaustible like muscle, rather than inexhaustible like medullated nerve. Brodie, on the other hand, finds that the splenic nerves, mainly composed of grey fibres, are as refractory to fatigue as are medullated nerves.

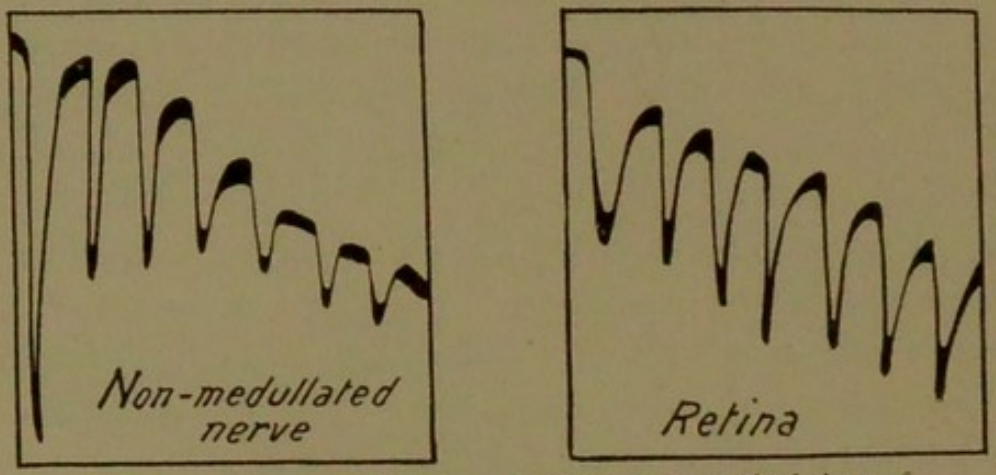


FIG. 21.—Non-medullated nerve shows more marked signs of fatigue than does the retina.

I should like in conclusion of this lecture to allude very briefly to the case of the retina. Judged by its electrical response to stimulation by light, the retina, like nerve, exhibits very great staying power ; there is little or no sign of fatigue during a long-continued series of luminous stimuli, and the same holds good of a series of electrical stimuli. There can, in the case of the retina, be hardly any doubt that the activity excited by light is a chemical function, and the chemical change is relatively considerable as compared with what is presumably the case for nerve. Its staying power must therefore be attributed to the effective restoration of expended matter rather than to an absence of expenditure.

We shall return to the problems offered to us by the retina in a future lecture.

[1] *Proceedings of the Royal Society*, vol. 66, p. 379, 1900.

P.S.—The restorative effect of oxygen. The work that has been carried out during the last few years at Göttingen under Verworn's direction, is in harmony with the data and conclusions set forth in this lecture. The action of CO_2 upon nerve, the production of CO_2 by nerve, the degree in which fatigue is experimentally demonstrable upon isolated nerve, are matters in which I am glad to find that the teaching of the Göttingen School is in substantial agreement with the statements and opinions that I have published during the last twenty-five years, and summarised from time to time in lectures (1897 and 1903) of which the present lectures (1909) are the continuation, as well as in successive editions of my *Introduction to Human Physiology* (1891, 1893 and 1896).[1] The principal difference between Verworn and myself consists in the fact that in general I regard excitability as being raised by CO_2 before it is lowered; whereas Verworn finds that CO_2 lowers excitability *ab initio*. The principal extension of knowledge brought forward by the Göttingen work consists in the demonstration of the part played by oxygen in the restorative phenomena of isolated nerve. On the human subject the restorative value of oxygen has been brought out very clearly by the recent observations of Leonard Hill on athletes.[2]

[1] An account of my first results on the matter was given in the form of reports to a Scholarships Committee of the British Medical Association (published in the *British Medical Journal* of July 1885 and July 1886). Their theoretical application to general neurology is considered in a paper on the "Sense of Effort," published in *Brain*, 1891, p. 179, also 1892, p. 329, and 1895, p. 200, and 1900, p. 1. The chief publications from Verworn's laboratory in the *Zeitschrift fur allgemeine Physiologie*, are by F. W. Fröhlich (1903, B. III. 75, 148; 1905, B. V. 288; 1909, B. IX. Ref. 1), by v. Baeyer (1903, B. II. 169, 180), and by Thörner (1908, B. VIII. 50; 1909, B. X. 29, 351).

[2] Hill and Flack, "The influence of Oxygen on Athletes." *Proceedings of the Physiological Society*, Jan. 23, 1909; in *Journal of Physiology*, 1909, vol. 38, p. xxviii.

LECTURE III

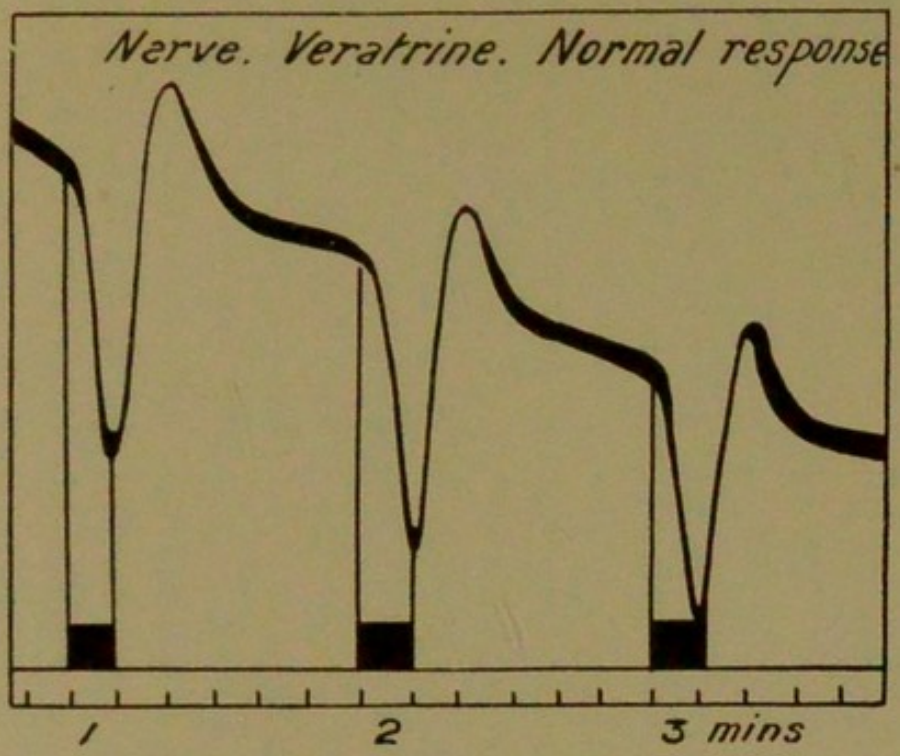
Veratrine, $C_{32}H_{49}NO_9$, and *Protoveratrine*, $C_{32}H_{51}NO_{11}$, are two closely-related alkaloids derived from green and from white hellebore respectively.

The former, as is well known, has a specific action upon muscle, causing its contraction to be extraordinarily prolonged ; the muscles of a veratrinised frog contract vigorously, and relax with extreme slowness. This characteristic effect occurs when the poison has been injected subcutaneously, and distributed to the system through the circulation, or when an excised muscle is immersed in a dilute solution of the drug. Whereas protoveratrine does nothing of the kind.

As regards the action of these two alkaloids upon isolated nerve, nothing definite is known, nor can well be known except by means of an electrical method as described in the first of these lectures.

If we remove the sciatic nerve of a veratrinised frog and examine it galvanometrically, we find that its response is perfectly normal. Whereas the sciatic nerve of a proto-veratrinised frog, examined in the same way, exhibits a very characteristic change—the negative variation is large and permanent, the positive after-deflection is abolished ; successive negative deflections are of diminishing magnitude, the nerve soon ceases to give any response whatever.

The theoretical bearings of the results are twofold—



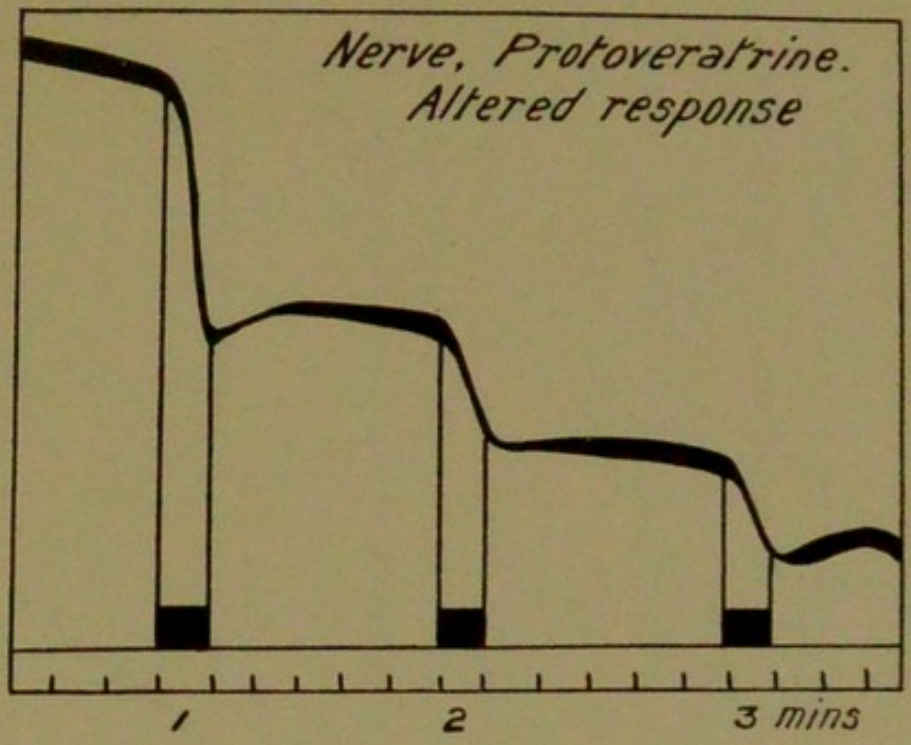


FIG. 22.

1. Three successive responses of an isolated sciatic of a veratrinised frog.

2. Three successive responses of an isolated sciatic of a protoveratrinised frog.

1. The facts in themselves furnish us with the clearest possible illustration of what we may call "fit and misfit" between each of two closely-related living tissues and each of two closely-related alkaloids. Veratrine fits muscle, not nerve. Protoveratrine fits nerve, not muscle.

2. The action of veratrine upon muscle and that of protoveratrine upon nerve can be brought together under the general principle considered in the previous lecture in

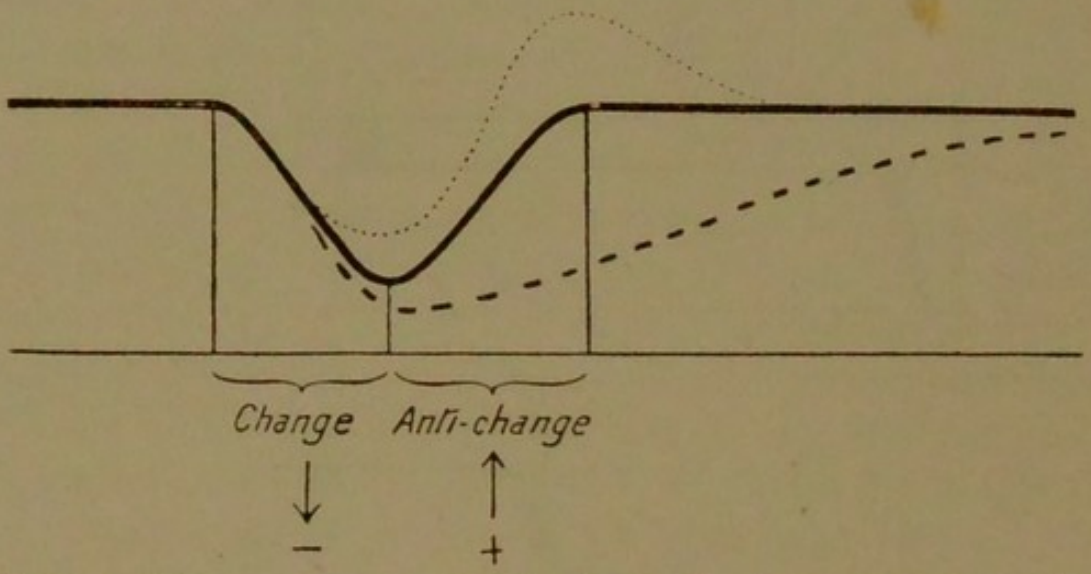


FIG. 23.—Diagram to represent an ideal reversible phenomenon—a muscular contraction or a single negative variation—as the effect of two opposed chemical movements. The consequence of a disfavoured anti-change is represented by the broken line; that of a favoured anti-change by the fine dotted line.

connection with the action of carbonic acid. We take as our point of departure that the primary chemical change aroused by excitation is *dissociation*, characterised by acidification and by a negative electrical movement (and in the case of muscle by contraction), and that this primary change is followed by a reverse chemical change or anti-change, as it may be called conveniently, involving de-acidification, and the return from negative to—or it may be beyond—the original electrical level previous to excitation (in the case of muscle, relaxation after contraction). The

alteration caused by veratrine in the case of muscle, or by protoveratrine in that of nerve, or, more generally, any alteration according to the type represented by the diagram (Fig. 23), may be taken to signify that, in consequence of the action of the alkaloid, the living matter of the muscle or of the nerve has been rendered less capable than normal of the secondary anti-change, which is expressed electrically as the positive return or after-effect.

We regard the negative and positive movements—the change and the anti-change—as being simultaneous rather than successive, the state of tissue at any instant being one of equilibration of two opposed forces, one or the other of which is temporarily dominant. Prolongation of the negative change takes place when, from any cause—*e.g.* carbonic acid or an anæsthetic or an alkaloid—the positive anti-change is disfavoured.

Through these considerations we are brought home to the axiom of general physiology to the effect that all living matter is the seat of two opposite tendencies—integrative and disintegrative, constructive and disruptive, anabolic and katabolic, positive and negative. We shall find this leading principle most clearly apparent in connection with the electrical response of the retina to light ; and in the case of green leaves we shall again have to recognise the double character of chemical change aroused under the influence of light.

Aconitine, $C_{35}H_{47}NO_{13}$, the alkaloid of monkshood, acts upon both nerve and muscle—on muscle like veratrine, on nerve like protoveratrine ; but I have not examined aconitine in this respect as closely as I have the two veratrine alkaloids. I have studied this alkaloid from a different point of view, *i.e.* in comparison with its two derivatives, benzaconine and aconine. The former is aconitine minus the acetyl radicle, the latter aconitine

minus the acetyl and benzoyl radicles. Their chemical relationship is as follows—

Aconitine, $C_{26}H_{39}(CH_3CO)(C_6H_5CO)NO_{11}$.
Benzaconine, $C_{26}H_{40}(C_6H_5CO)NO_{11}$.
Aconine, $C_{26}H_{41}NO_{11}$.

Benzaconine in relation to muscle and nerve is far less active than aconitine. Aconine is still less so. The peculiar toxicity of aconitine appears therefore to depend on the presence of the acetyl group, CH_3CO.

My interest in the study of aconitine was first aroused over thirty years ago by a notorious case of poisoning. Lamson studied at Edinburgh in 1877, at the same time as I did. At that time the teaching was that aconitine is a powerful poison undiscoverable *post mortem*. In the following year its presence in the alimentary canal of one of Lamson's victims was proved by a physiological test, *i. e.* by the lethal effects upon mice of the contents of the alimentary canal. As a matter of fact, aconitine, so far from being undiscoverable after death, is one of the most readily-identified poisons—not, however, by chemical but only by physiological tests—and for the purpose of identification there is no better physiological test than by the tip of one's own tongue. Dip the tip of a finger in a medicinal solution of aconitine diluted a hundred times and apply it to the tip of your own tongue, and, if the medicinal solution is good, you will never fail to recognise the characteristic and prolonged tingling sensation. Aconitine by reason of its extreme toxicity is detected physiologically where chemical tests are too coarse. Its intense local action on sensory nerve-endings, and on nerve and on muscle, are all of a piece with its intense general toxicity. Testing by the muscle-method, as described in the First Lecture, I find that the toxicity of a

molecule of aconitine is more than a hundred times that of a molecule of chloroform, and that the effect of aconitine, once produced, cannot be removed.

One of the most elementary problems that we may set ourselves to resolve, in the case of an excitable tissue such as muscle or nerve, is to determine how much responsive effect follows upon an exciting cause of increasing magnitude.

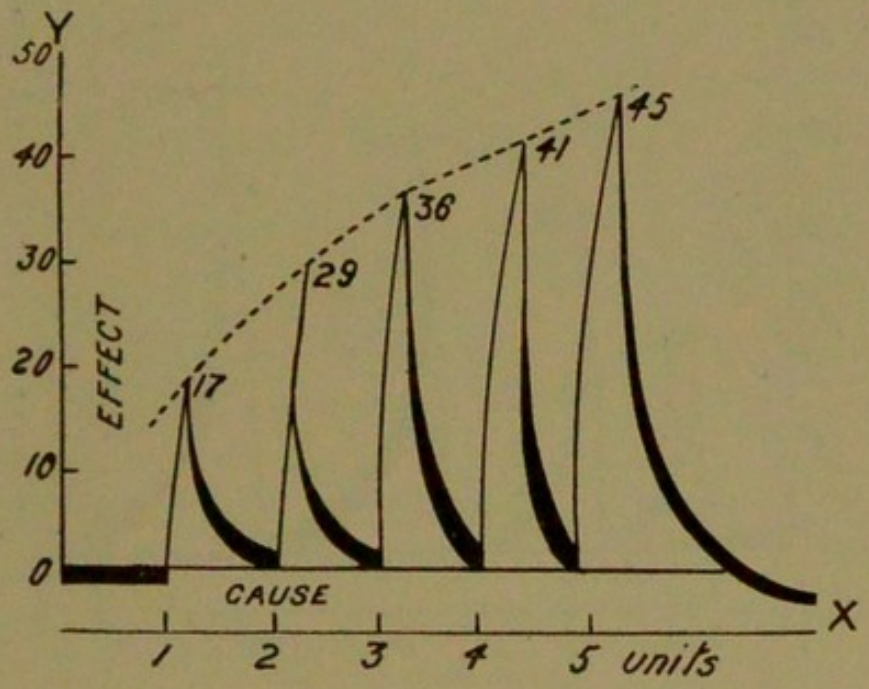


FIG. 24.—Increasing magnitudes of muscular contractions caused by tetanisations of arithmetically increasing magnitudes.

We can conveniently summarise our results by plotting a curve, marking off magnitudes of cause or excitation along the X axis, and magnitudes of effect along the Y axis. Let us say, for instance, that with a series of stimuli of arithmetically increasing magnitudes = 1, 2, 3, 4, 5, we have obtained contractions = 17, 29, 36, 41, and 45 millimetres, we should plot the cause / effect curve as follows, viz. concave towards the abscissa OX, with diminishing increments of effect + 12, + 7, + 5, + 4, caused by equal increments of excitation.

Or, to take another case, where the cause was electrical stimulation, and the effect an electrical response of the retina (Fig. 25).

In both these instances the curve obtained by joining the tops of the contractions, or of the deflections, is concave towards the axis OX, *i. e.* with equal increments of exciting cause, there have been diminishing increments of effect.

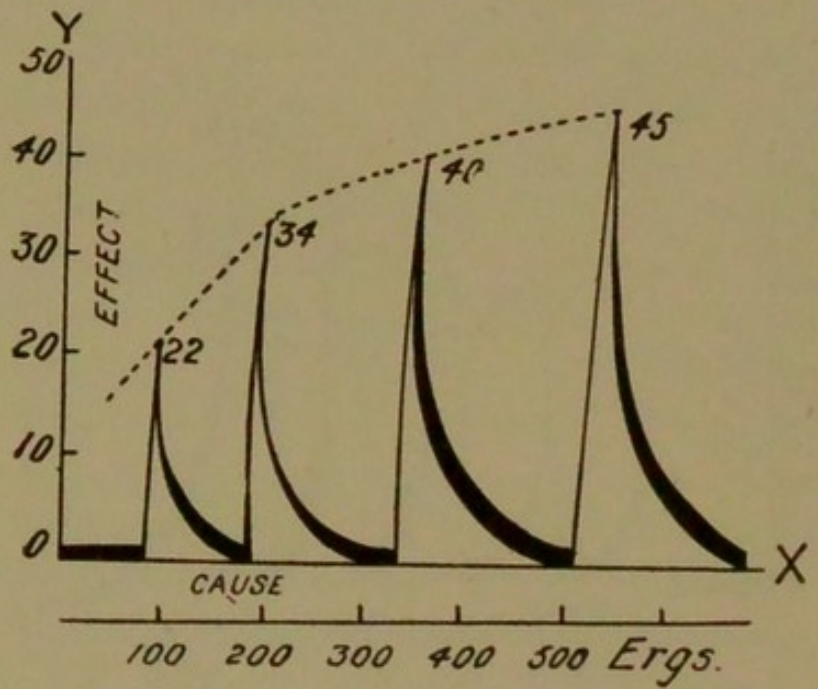


FIG. 25.—Here the values of X were 80, 180, 320, and 500 ergs, and the values of Y were 22, 34, 40, and 45 scale units, *i. e.* the increments, 12, 6 and 5.

The result recalls to mind the similar results from which the psycho-physical law of sensation was originally derived, through the observations of Weber, and the still more elaborate observations and calculations of Fechner. According to this law, equal increments of sensation require geometrically increasing increments of stimulation; or, otherwise put, diminishing increments of sensation are caused by equal increments of stimulation. Within the ordinary range of our every-day experience we are all of us familiar with something like this relation;

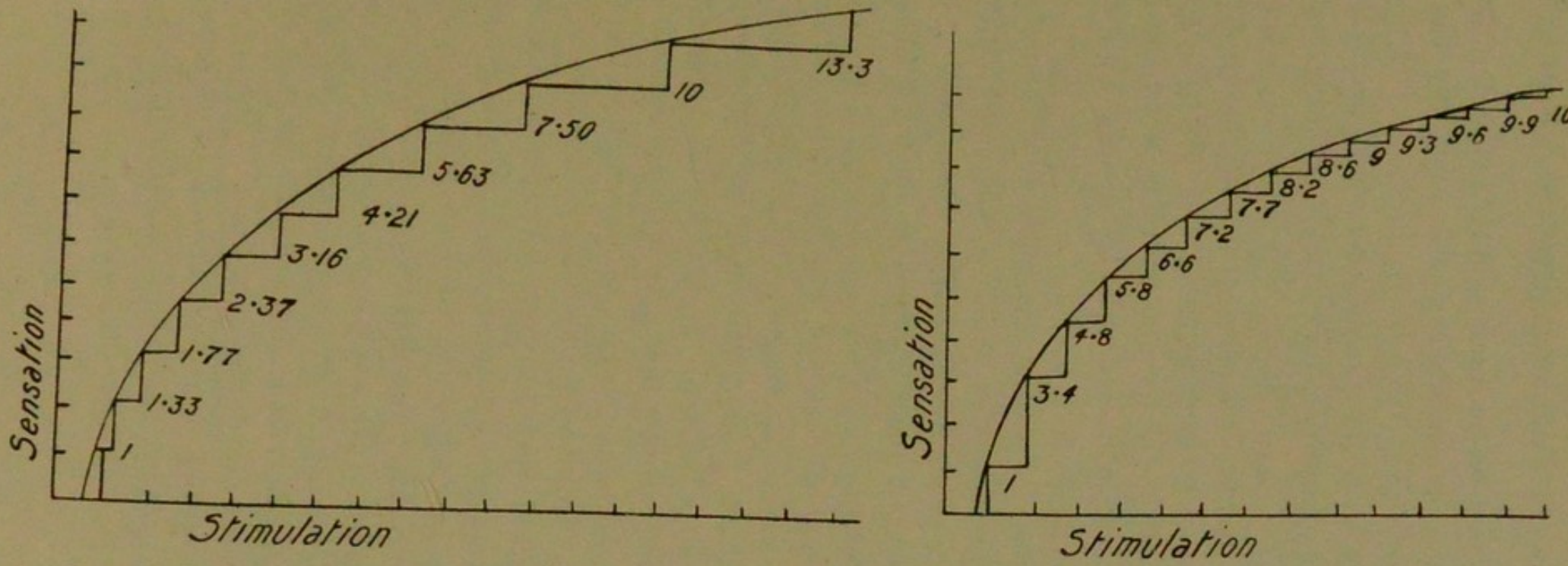


FIG. 26.—Curves to represent increasing magnitudes of sensation caused by increasing magnitudes of stimulation. In the left-hand (upper) curve the sensation increments are represented in terms of equal increments caused by increasing increments of stimulus. In the right-hand (lower) curve the sensation increments are represented in terms of diminishing increments caused by equal increments of stimulus. The two curves are identical.

the cause / effect curve between stimulation and sensation is normally concave towards the base line, like the two preceding curves [1] (Fig. 26).

But they are very short, and when we reflect further, we are led to amplify and modify this elementary conception.

We realise, in the first place, that the psycho-physical relation expressed mathematically, and sayings such as that of Laplace—"La fortune morale varie comme le logarithme de la fortune physique"—do not embrace all the facts of sensation.

And then we realise that the relation—whether logarithmic or otherwise—is not of necessity psycho-physical at all, but more probably physical or chemical.

We shall find it worth while to consider these two objections separately—

The curve concave to the abscissa, while fitting the facts of all ordinary experience in which equal increments of objective cause give diminishing increments of subjective effect, does not truly represent our relation to the excessively weak stimuli that give us our weakest sensations. At this lowest range the increments are not at their greatest, diminishing thereafter in the ascent of the scale—that would imply at this lowest range a state of hyperæsthesia most exquisitely intolerable and unnatural—but at their smallest; the curve of sensation does not spring at once concave towards its abscissa OX, it arises at first convex towards the abscissa by increments smallest at first, then increasing to their maximum, subsequently diminishing, precisely in accordance with the facts observed in certain cases of rate of chemical change (Fig. 27). You understand now, that a given increment of objective cause brings about greatest increment of subjective effect, *i. e.*

[1] Appendix, Note 3.

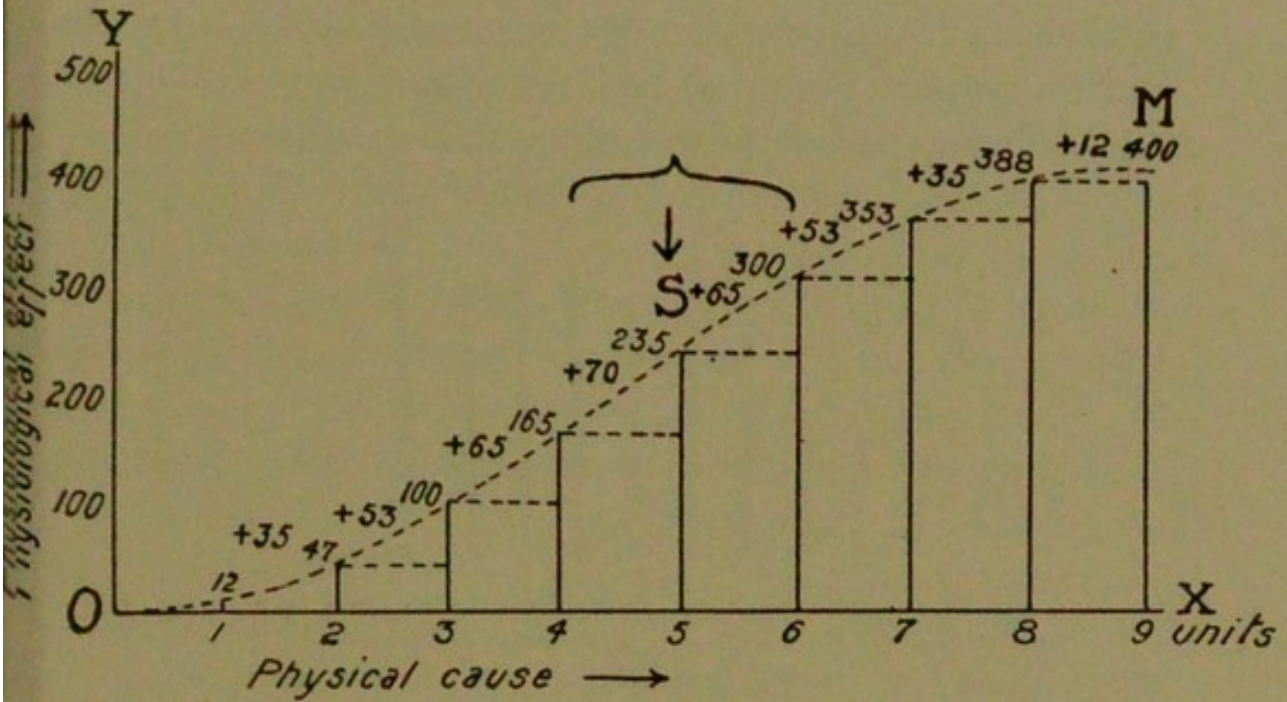


FIG. 27.—An S-shaped curve to represent a physiological effect of a physical cause increasing by equal increments. The increments of effect are smallest at first, increase to a maximum at S, and subsequently diminish.

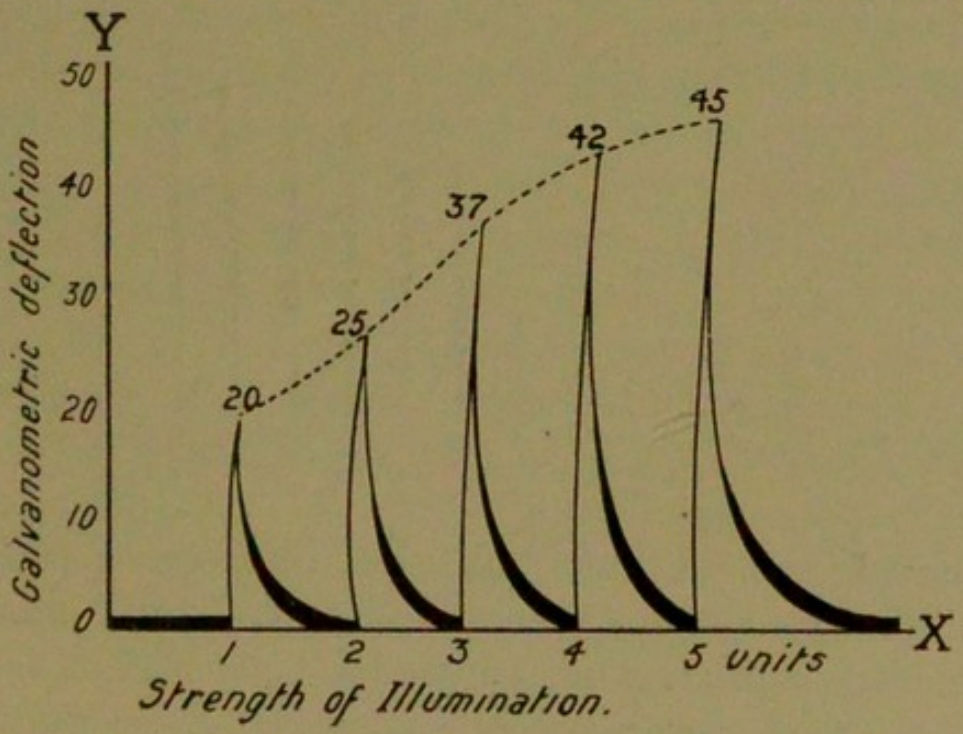


FIG. 28.—Magnitudes of five retinal responses to luminous excitations of arithmetically increasing magnitudes. An approach to an S-shaped curve is apparent.

of sensation—not at the very beginning of the effect, but further on in its course. We are most sensitive to the multitudinous stimuli of our environment when these stimuli have reached a measurable, *i. e.* a moderate, value,

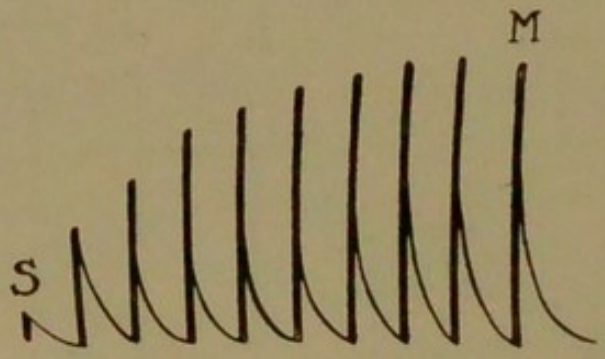


FIG. 29.—A series of muscular contractions in response to a series of excitations of arithmetically increasing magnitude in which an S shaped curve is not apparent.

not when they are of infinitesimal magnitude. Otherwise we could not live.

At the other end of the scale, as we approach maximal values of stimulation and sensation, increments of sensation

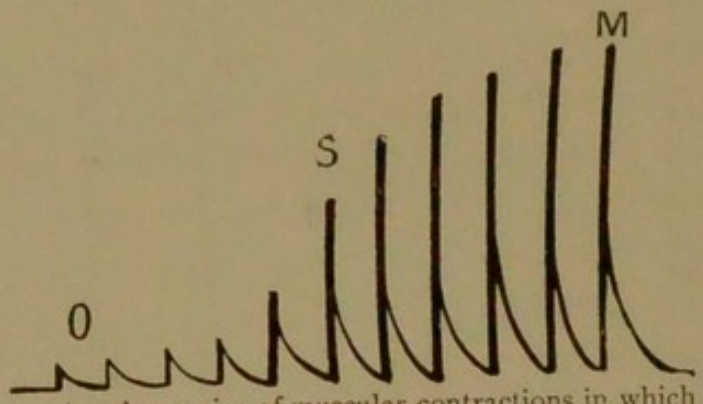


FIG. 30.—Another series of muscular contractions in which an S-shaped curve is apparent.

by equal increments of stimulation, continue to diminish, until finally sensation becomes pain, and actual injury of tissue takes place. If stimulation is increased beyond the point of maximum sensation, the latter declines; with unlimited stimulation, pain itself reaches a limit, and terminates in zero sensation, when injury of tissue has

resulted in destruction of tissue. But such ultra-maximal effects are beyond the range of any law of sensation, which we must practically take as being applicable only between the limits of minimal and maximal sensation.

Within this range we have distinguished two portions: a first shorter portion at the minimal end, in which equal increments of stimulus cause increasing increments of sensation; a second longer portion, in which equal increments of stimulus cause diminishing increments of sensation. The first portion of the plotted curve is convex to the base line OX, the remainder is concave; so that the entire curve has an S-shaped or sigmoid character, the turning-point of which—where the increment of sensation is greatest—is the point of most acute sensitiveness; it is an optimum in the middle of the region of weak stimulation where our sensory judgments are at their finest (Fig. 27).

But is the relation in reality psycho-physical? Between the external physical stimulus and the final subjective sensation we have to recognise the internal physiological change—presumably of a chemical nature—taking place in the peripheral and central nerve-terminals, and constituting the immediate antecedent of sensation—the sensificatory change or internal stimulus to which sensation is attached. Or, otherwise expressed, between the objective stimulus A and the subjective sensation C, we have to recognise the existence of a physiological change B. The external stimulus A causes the physiological change B, which is the basis of the sensation C, and in this sequence ABC we have seen that equal increments of A arouse decreasing increments of C, so that with unlimited increase of the stimulus A there is limitation of the sensation C. Is this limitation of the final effect C, by limitation of the physiological change B, or by limita-

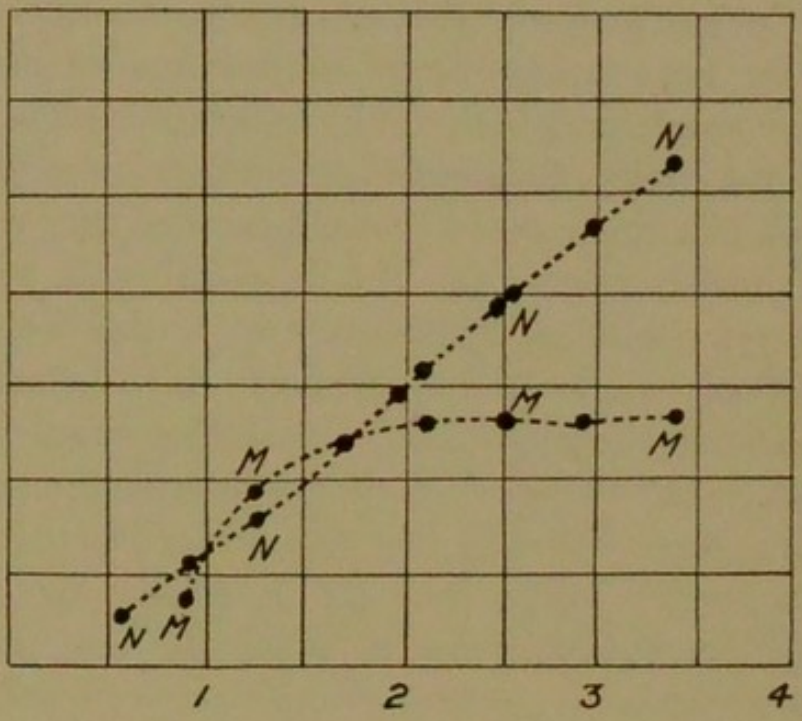


FIG. 31.—A diagram on which are plotted the values of muscular responses M, M, M, and of nerve responses N, N, N, to stimuli of arithmetically increasing magnitudes applied to the nerve. The former soon reached their maximum. The latter, within the range of the experiment, continue to increase in an approximately straight line up to between 3 and 4 units.

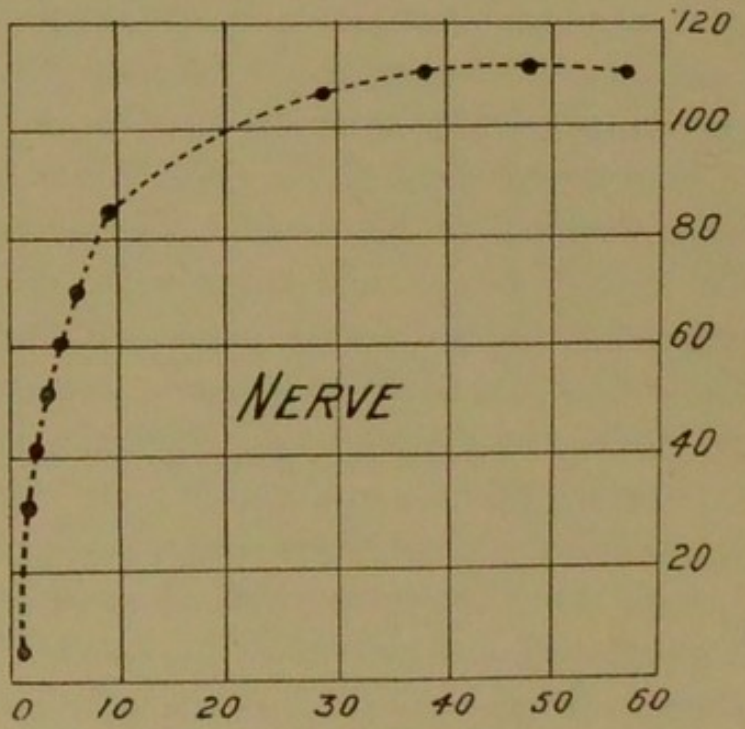


FIG. 32.—Continuation of the previous experiment on nerve with further increase in the strength of stimulation up to between 50 and 60 units shows that in this case also a maximum is reached.

tion of the psychical result C, producible by B? Otherwise stated, does the limitation take place between A and B or between B and C?

In every instance known to me, where the physiological effects of excitation are experimentally accessible, I find that equal increments of excitation A arouse diminishing increments of physiological effect B. It is so in the case of nerve, and in that of muscle, when we plot magnitudes of excitation along the X axis, and magnitudes of response, either electrical or mechanical, along the Y axis. An S-shaped curve, OSM, Fig. 30, convex then concave, or, failing the entire curve, at least its main concave portion SM, can be recognised as expressing the general relation between physical cause and physiological effect.

This relation is most recognisable in the case of the Retina (Fig. 28) and in that of Muscle (Fig. 30). It is less recognisable in that of Nerve, at least under the conditions of my experiments, which however have brought out the rather striking fact that a maximum effect in the nerve itself requires a stimulation intensity far above what is sufficient to bring out the maximum functional effect in the attached muscle. Thus, as is illustrated by the data plotted in Figs. 31 and 32, excitation of a nerve gave maximal muscular action at an intensity of 2 to 3 units, whereas maximal action of the nerve itself required an intensity of 40 to 50 units.

Taking another case—the curve of declining electrical response of a nerve under the gradual uniform influence of an anæsthetic vapour—we find that the response declines slowly, then faster, then slowly again, until it disappears completely, *i. e.* according to a sigmoid curve. Taking now the curve of recovering response of the anæsthetised nerve replaced in ordinary air, we find that

this occurs slowly, then faster, then more slowly, until it is completed, *i. e.* along a sigmoid curve.

And now it becomes apparent to us that in these two physiological events of incorporation and dissipation of an anæsthetic by protoplasm, we are dealing with a physico-chemical change that can be symbolised on the reversible type—

Chloroformed Protoplasm ⇄ *Protoplasm* + *Chloroform*,

and of which the curve in either direction must be in accordance with the law of diminishing increments with diminishing differences of tension.

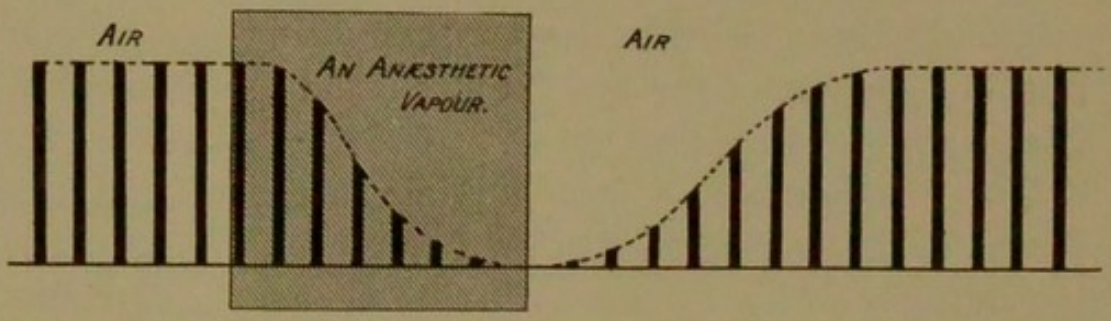


FIG. 33.—Diagram representing a series of normal responses of isolated nerve before, during, and after the action of chloroform vapour at 2 %. The curve of anæsthesia and that of recovery from anæsthesia are both of an S-shaped character.

From the standpoint thus arrived at, there can be little doubt that the Weber-Fechner logarithmic law, given as representing the relation between excitation and sensation, is not in reality psycho-physical, and that it does not present us with any numerical ratio between matter and mind. The curve and the various formulæ derived from it are essentially a portion of the far more general relation between magnitude of cause and magnitude of effect in the domain of physical chemistry to which all changing and changeable matter—inclusive of living matter—belongs.

The Weber-Fechner curve does not bridge the gulf from physical to psychical ; it is from physical to physical.

As to the final ratio between physical and psychical, we have no evidence ; we have never measured the sensificatory change B behind the sensation C, and in the absence of such measurement we are free to accept that the ratio between increments of B and increments of C is the simplest possible, viz. arithmetical—indeed, on the principle of greatest economy of hypothesis, and in the absence of evidence to the contrary, we ought to assume this, and to take it that sensificatory changes B, 2B, 3B, etc., give sensations C, 2C, 3C, etc.

The first and second portions of our S-shaped curve (Fig. 27) represent in this province the division of chemical change into (1) an initial "period of induction" during which acceleration of rate of change takes place, and (2) a subsequent logarithmic period during which the rate of change becomes slower.

In conclusion of these considerations let us examine some of their applications to educational theory—to the rate at which new knowledge and skill are acquired—to the rate at which memories fade away.

I think that most of us have at some time in our life experienced that the acquisition of new knowledge, such as that of a language or of a game of skill, has required the greatest effort of application for the first steps achieved from the state of zero knowledge : "Ce n'est que le premier pas qui coûte ;" and that, once this first difficult stage has been traversed, our further progress is comparatively easy and rapid, at relatively small cost of effort and application. The easiest part of our task, that in which the smallest effort gives the greatest upward progress, is its middle portion. And then progress slackens, our later and our last steps towards a perfection that we never reach, cost voluntary energy far in excess of that required by the easier steps taken within the

range of mediocrity. The two hardest and most expensive stages of our achievement are its beginning and its end. "Ce n'est que le dernier pas qui coûte" is as true a saying as "Ce n'est que le premier pas qui coûte."

But the collection of numerical data from which to construct an acquisition curve is by no means an attractive task. It is one of those dreary mechanical tasks of which the chief service is to test the mettle of the novice, whose first lesson in any science should be that great effort is necessary for small result.

Ebbinghaus has counted the number of times 2, 3, 4, etc., non-sense syllables have to be read over before they can be repeated from memory without fault. Plotting as our cause along OX the minimum number of repetitions required (or their time) and as our effect along OY numbers of syllables remembered, the curve came out roughly of a sigmoid type; increments of result, poorest at first, increased and then decreased; the curve was convex then concave to its base line. "Ce sont les premiers et les derniers pas qui coûtent le plus." But the methodical study of non-sense syllables is a repulsive task. Even its first step—the preparation of a non-sense set of syllables, free of associative links with each other by sound or rhythm or unintended sense—costs more time and thought than might have been anticipated. And, as far as I know, no one since those results were published has possessed sufficient energy and doggedness to repeat the task.

Casting about for some not too tedious form of work amenable to numerical treatment, it has occurred to me that the game of billiards lends itself better than most other games to the requirements of the psycho-physicist, affording as it does a fairly monotonous yet not too repulsive series of trials of skill that can be broken up

into groups for psychometric purposes. Apart from any differences of skill attributable to idiosyncrasy or to previous experience, we can take in the case of an absolutely inexperienced person on successive days the quotient $\frac{\text{hits}}{\text{hits} + \text{misses}}$ of any selected stroke, and obtain for that person the gradually rising quotient indicative of increasing skill, with unity or perfection as the asymptote of the increasing fraction. And even if the subject of experiment be not absolutely inexperienced at the outset of trial, or if with increasing skill the student under observation should find it less tedious to apply his skill

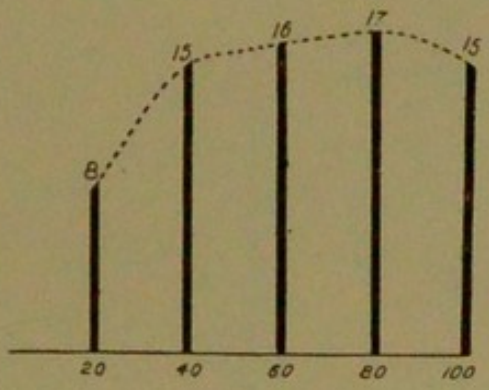


FIG. 34.

in the ordinary haphazard manner, still we might expect that chance fluctuations would vanish in presence of the large numbers of trials available for statistical purposes. I made 100 trials the other day on such a person, broken up into 5 groups of 20 each, just to see whether the plan was likely to afford any rational result. The total number of trials was of course too small, yet small as it was, I think the result was sufficiently reasonable to make it worth while to test the plan by larger numbers of trials. Here are the actual numbers :—8 hits in the first group of 20 trials, 15 in the second group of 20, 16 in the third, 17 in the fourth, 15 in the fifth, and the subject was distinctly tired at the end of the 100 trials.

The rate at which we forget can likewise be expressed as a falling curve with time taken as the abscissa OX. I think it must be within the experience of most of us who have observed ourselves that our forgetting is done very quickly to begin with, and then very slowly. A secretary of committee keeps a fuller and more faithful record of proceedings if he writes up his minutes at each meeting

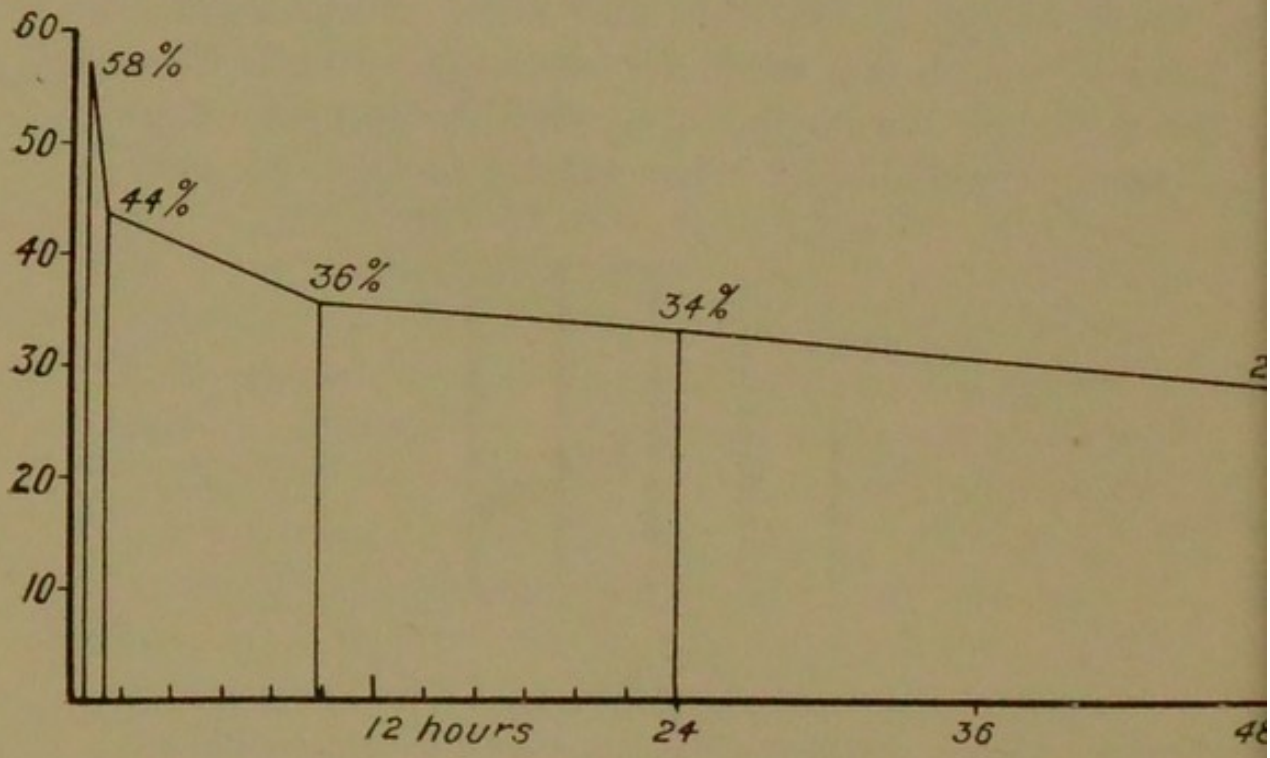


FIG. 35.—Memory curve after Ebbinghaus (*Das Gedächtnis*, Leipzig, 1885). The ordinates signify the percentages of syllables remembered at the end of 20 minutes, 1 hour, 9, 24, and 48 hours. From this period onwards the percentages (not indicated in this diagram) were 25 and 21 at the end of 6 and 30 days.

than if he puts it off till next day, and if he puts it off for one day he does not lose much more by waiting two or three days longer. The rate at which his cerebral memory image wears out may be represented in concrete form by the curve constructed from systematically observed data taken of the residual numbers of non-sense syllables remaining in memory at varying intervals of time after they have been perfectly memorised. Thus at the end of 1

hour the loss is over 50 per 100, at the end of 9 hours over 60 per 100, at the end of 30 days 80 per 100. But, as we all know, memories differ, and their measurements can hardly be carried out with scientific precision.

I attach a very general significance to the S-shaped curve given in Fig. 27. It is in my thought the life-curve *par excellence*. In art it is the "line of beauty." In science it is the line of response. Excited movement begins slowly, proceeds faster, and ceases slowly—like the swing of a falling and then rising pendulum. And in the

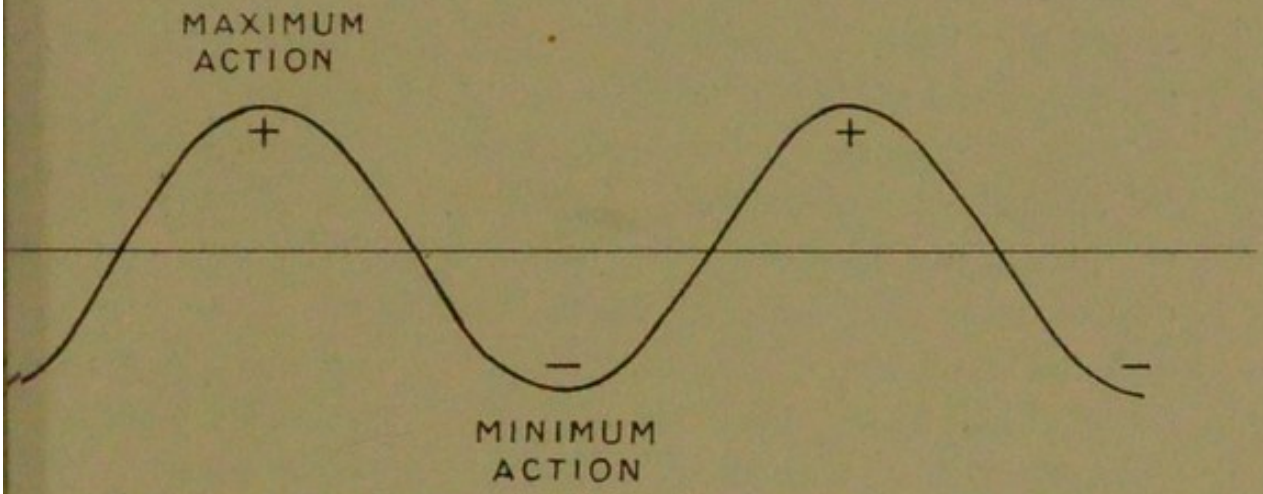


FIG. 36.—A harmonic curve (curve of sines) to represent an ideal rhythmic action. The curve is S-shaped from + to − and from − to +.

waxing and waning movements that compose the manifold rhythms and pulsations of living matter, the same harmonic law may be discerned throughout the alternation of slow—fast, resting—active. The rate of movement from least active to most active, and from most active to least active, increases and decreases according to an S-shaped curve.

LECTURE IV

We have reached a crucial point in these lectures. I have already more than once alluded to the retina. Its study has been to me a kind of nodal point at which several lines of thought have come to their focus, and from which lines of further information have diverged in altogether unexpected directions. Let me attempt to retrace my steps and to go over again with you some of the paths that led to the best outlook.

I came to the retina in the course of an attempt to discover signs of electrical effects in the human brain coincident with the physiological changes of which our sensations are the subjective evidence. I did not succeed in this attempt—and let me say in passing that I do not regard any of the results described by other observers on the matter as being at all convincing—but in the course of trials made with luminous excitation, I obtained electrical changes that appeared to be of retinal origin. This made me pursue the study of the electrical effects of light on the isolated retina and on the isolated eyeball, and I published the results in due course.[1]

The retinal blaze.—I wanted to know, in the first place, whether mechanical and electrical excitation of the eyeball would elicit electrical effects like those caused by luminous

[1] "On the Retinal Currents of the Frog's Eye, excited by Light and excited Electrically," *Phil. Trans. R. S. B.*, vol. 193, p. 123, 1900.

stimulation. I found that they did. The effects were indeed of altogether surprising magnitude and duration.[1]

We know that a blow upon the eyeball, or a steady mechanical pressure, or an electrical current, elicits subjectively a blaze of light—a phosphene. This led me to use the term "blaze-current" for the objective electrical effect elicited by mechanical and by electrical excitation of the eyeball. From all we know about the action of light upon the retina we cannot doubt that a blaze-current is the electrical expression of a chemical change.

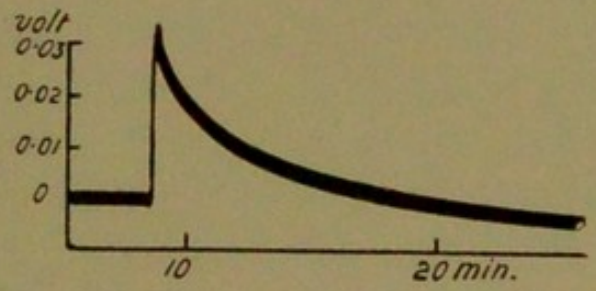


FIG. 37.—A typical blaze-current of the eyeball in response to electrical excitation. The excitation was of positive direction, *i. e.* from fundus to cornea; the response is in the same direction. Its electromotive force is over 0·03 volt, and its duration upwards of ten minutes.

The lens.—The next thing I found was that a blaze-current was not exclusively retinal, but that it can be elicited from other parts of the eyeball. The crystalline lens in particular gives a very remarkable blaze-current, about which I shall have something to say later.[2]

And now the path divided into two, and both the new trails were equally attractive.

Green leaves.—On the one hand, the mere anatomical difficulty of separating the retina from the eyeball without injury led me to wish for a natural sheet of living matter

[1] "On the 'Blaze-currents' of the Frog's Eyeball," *Phil. Trans. R. S. B.*, vol. 194, p. 183, 1901.

[2] "On the 'Blaze-currents' of the Crystalline Lens," *Proc. R. S.*, Dec. 4, 1902.

in which electrical signs of chemical action excited by light might be looked for and studied. This made me examine the action of light on green leaves.[1] I found what I was looking for at once, and spent more than a year upon the study of the electrical effects of light upon green leaves. And then this trail came out into the same clearing that the lens trail had led to. The electrical response to light was a sign of life in the case of a green leaf—dead leaves give no such response. Was it dependent on the presence of chlorophyl? Would the petals of flowers respond to light? No, they did not do so, that was sure; yet equally surely the flower is alive, though it does not answer to light; there *must* be some way or other of getting a flower petal to show whether it is alive or not. How about blaze-currents? They indicate in the case of the lens, where one would otherwise be at great loss how to find out whether the stuff is alive or dead; will they indicate in the case of a flower petal?

Flower petals.—The result of the trial was immediately and completely satisfactory; the petal of a living flower gave a large blaze-current, which disappeared when the flower was killed or exhausted, and from this I was led on to devise what I regard as a representative experiment and have called the experiment of the electrocuted lily. I shall describe and, I hope, show this experiment presently. But let me finish this story first.

From the retina to the crystalline lens—from the retina to a green leaf—from the green leaf to a flower petal, our trail has been plain, and has taught us a sign by which we may hope to penetrate further into the jungle. It looks as if we might use the blaze-test as a general test, to tell us whether or no a given bit of stuff is living, and

[1] "The Electrical Effect of Light on Green Leaves," *Proc. R. S.*, vol. 67, p. 129, June 14, 1900.

if it is living, how much it is living—whether it is at par or above par or below par. In point of fact I very soon found that the test was of quantitative as well as of qualitative application, at least upon the one or two selected instances in which time has permitted me to make a sufficient number of trials. The two instances in which this has been done are: seeds as representing vegetable tissues—the human skin as representing animal tissues. For the purpose of to-day's demonstration I intend to compare a ripe (yellow) apple with an unripe (green) apple.

But, to use a colloquialism that has become very familiar to me in the last few weeks, we are up against a big proposition. Here is a new test, the systematic use of which promises to afford a measure of vitality for animal and vegetable tissues. The effort of a single person to work a claim of this size counts for very little. I have only been able to work out two or three tissues, sufficiently far to warn me not to generalise too hastily and conclude that *all* animal and vegetable tissues are alike amenable to the test. Some are more amenable than others; why and wherefore, I am unable at this stage to say. The physical and chemical and physiological conditions of the test will require much patient study before a clear understanding of them is arrived at.

I shall attempt to cover no more than a small fragment of the ground, and that only by a very cursory survey. Retina, Lens, Leaves, Petals, Skin, Seeds, Fruits, Eggs—any one of these subjects, in respect of the considerations with which we are now occupied, would require more than an hour's lecture to be dealt with properly. But the pith of the matter, simplified and expurgated of debatable points, can, I think, be profitably presented.

Photo-electrical response of the retina.—We all know that the retina is excited by light; the result of such excitation is subjectively a visual sensation, objectively an electrical change, together with certain other physical effects upon which I need not dwell at present.

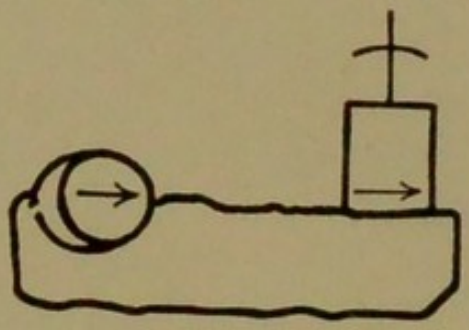


FIG. 38.—Diagram to illustrate the positive direction of retinal currents, *i. e.* from fundus to cornea.

The electrical change in the normal eye—the excised eye of the frog—is of the following character:—During illumination there is a current in the eyeball from back to

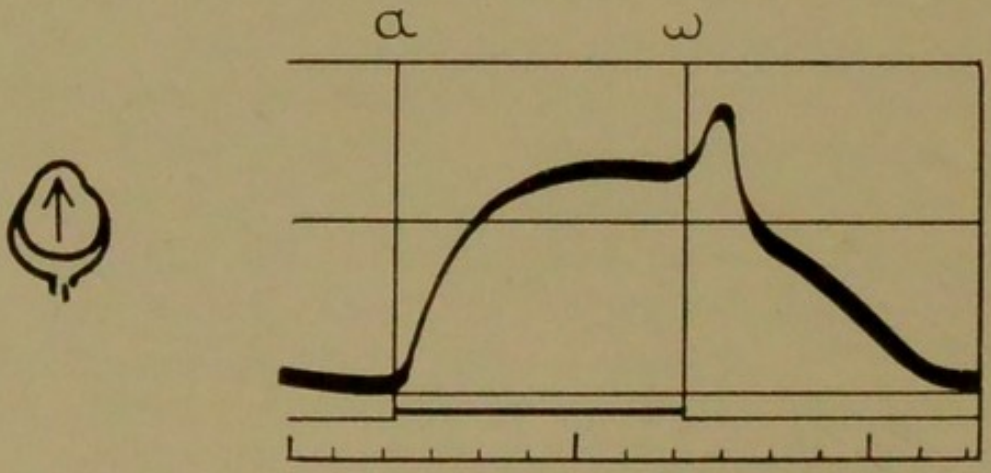


FIG. 39.—A normal electrical response of the retina to illumination commencing at α and ending at ω, lasting for one minute.

front, or, as we may call it, in a positive direction. This current makes its appearance at the commencement of illumination, and continues during illumination, and is suddenly augmented at the end of illumination.

The first feature that arrests attention is that the deflec-

tion at ω has the same direction as that at α. At first sight it looks as if light gave a "break" excitation at ω, as well as a "make" excitation at α; but on further reflection and examination, this similarity with make and break effects of a galvanic current in the case of nerve and muscle must be recognised as being superficial and illusory. There is no real correspondence between the make and break effects of light on the retina, and the kathodic make and anodic break effects on muscle, although

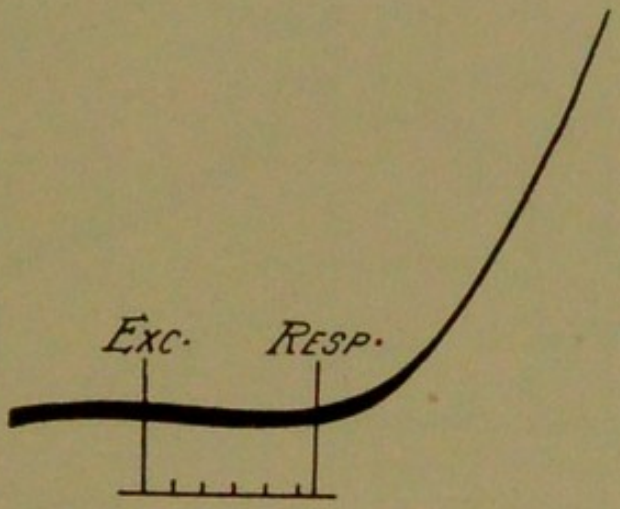


FIG. 40.—A retinal response to light recorded on a more rapidly travelling surface, showing the period of hesitation, in this instance about five seconds, at the commencement of illumination.

superficially the two sets of effects are so similar. The explanation of the retinal response is to be looked for on a very different basis.

We shall be in a better position to understand this when we have looked more closely into what occurs at the commencement of illumination. Here there are two remarkable features, one or other of which is the more prominent according as a more or less rapid galvanometer is employed. With an ordinary mirror galvanometer and its comparatively heavy equipage, the positive deflection at α may be extraordinarily delayed. This delay, which in extreme cases may amount to several seconds,

cannot be regarded as a true latent period; I have characterised it as being a period of hesitation during which two opposed currents pass through the galvanometer. And sometimes—even with a sluggish instrument—we may get a photograph that shows more or less plainly that there is at α a short negative deflection preceding and quickly overpowered by the more prominent positive deflection. Einthoven, by means of his

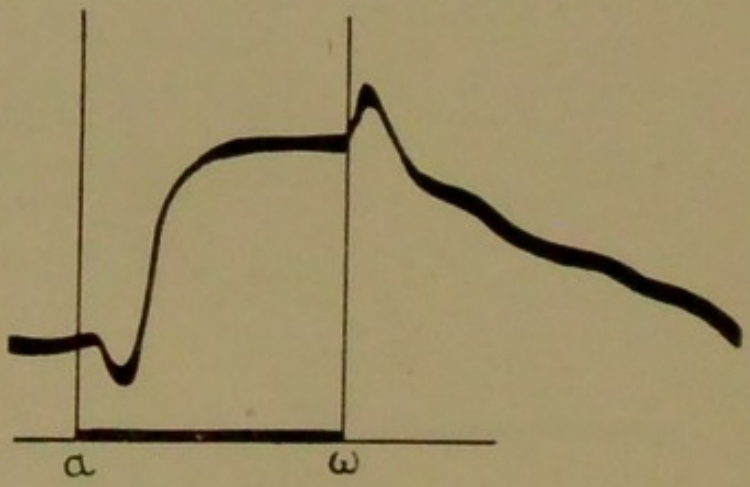


FIG. 41.—A retinal response to light, exhibiting a brief negative deflection at α, followed by the main positive deflection during illumination at its termination ω.

extremely rapid galvanometer, has shown that this brief negative effect at α is a regular feature of the normal response.

We are now in a position to appreciate, as the probable explanation of the normal retinal response to light, the analysis which Fig. 42 is given to illustrate. The normal response, mainly positive, is the resultant of two opposed changes—of a negative change beginning and ending rapidly and of a larger positive change beginning and ending more slowly. Let me remark in passing that I regard this composite effect of light upon the retina as an illustration of the axiom alluded to above, to the effect that

living matter is the seat of two opposed chemical movements. During the intensification of the living state aroused in the retina by light, both of the opposed changes become manifest.

Admitting as a fact—apart from any theory—that the normal retinal deflection is composed of two opposite

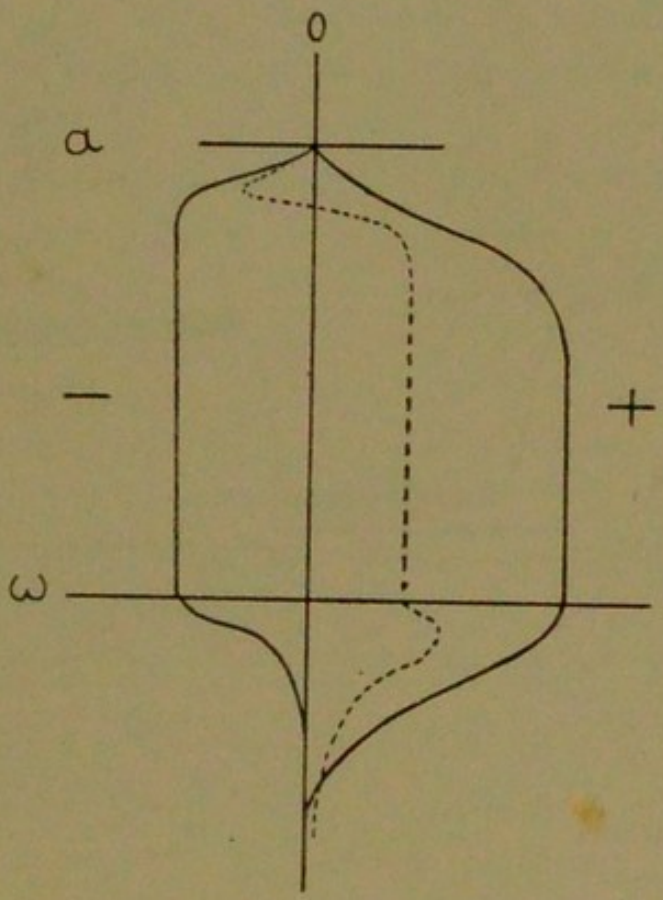


FIG. 42.—Diagram to exhibit the composition of a normal retinal response (dotted line) by a positive and a negative component, as explained in the text.

effects, we are naturally led to inquire whether these two effects can be dissociated by experimental means. They can. An eyeball carefully prepared, and giving therefore a normal positive deflection, gives a negative deflection after it has been submitted to moderate pressure, or to electrical tetanisation of considerable strength. By either of these means the capability of the retina to manifest

positive change has been disfavoured, and its capability to manifest negative change has thereby been unmasked.

The true latent period of the retinal response to light, although its value does not come anywhere near that of the period of hesitation, is yet of considerable magnitude, *i.e.* 0·15 to 0·20 sec. The latent period of a positive response of an eyeball before massage is slightly longer than that of the negative response of the same eyeball after massage—0·16 sec. in the former case, 0·12 sec. in the latter.

Excitation of the eyeball by mechanical or by electrical

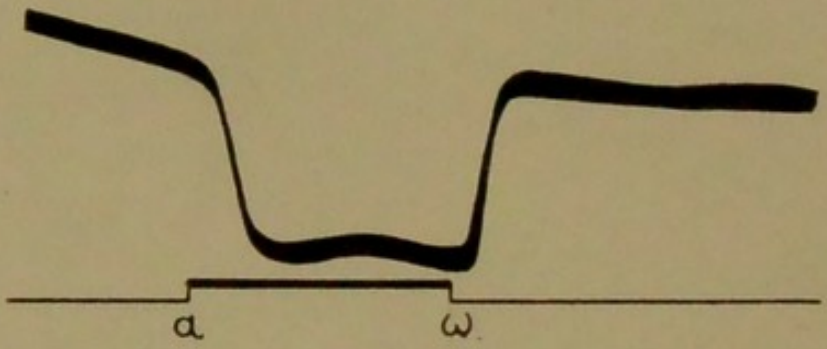


FIG. 43.—A retinal response to light subsequent to massage of the eyeball. The normal positive response has given place to a pure negative response.

stimulation acts like light, producing a positive retinal current. After mechanical pressure—"massage" of the eyeball—the positive response to light is replaced by a negative response (Fig. 43).

Our preconceived notions as to the extreme delicacy of the retina are indeed somewhat rudely shocked by the great strengths of current that it can withstand, and yet remain excitable by light.[1] This seems to indicate the presence of some photo-chemical change persisting in the retinal pigment independently of the living state. But I have not yet put this point to the test of further experiment, and shall therefore not dwell upon it now. The

[1] *Proceedings of the Physiological Society*, June 17, 1905.

centre of our attention is the electrical effect of electrical excitation—or, as I have termed it, the blaze-current.

The blaze-current is not restricted to the retina ; it is exhibited in quite remarkable degree by the crystalline lens ; in which, as well as in the retina, it is completely abolished by strong electrical currents.

The crystalline lens.—In the course of these investigations my attention was aroused to the fact that the anterior half of the eyeball often gave a larger blaze response than did the posterior half. The effect was traced back to the crystalline lens, and during an autumn holiday at the seaside I took a large number of observations on the eyes of freshly-caught fish. The blaze-currents under such conditions were very regular and of constant direction—from the anterior to the posterior pole through the lens—and they were abolished by heat, by strong electrical excitation, and by mechanical pressure.[1]

On returning to London I continued the observations on fish as received from the fishmongers—on cod and on salmon—and I obtained very irregular and unsatisfactory results—frequently no response at all. This seemed odd, all the more so in that I had previously noticed the great endurance of the reaction in the series of observations made near the sea. Then a newspaper advertisement, "Living fish fresh from the sea," caught my eye, and the matter was very soon cleared up. The so-called "living fish" never failed to supply me with a couple of active lenses. Yet the eyes of fish as received from fishmongers were as bad as ever. I have no doubt now that this was owing to the fish having been frozen, as I found that the reaction was permanently abolished after congelation of

[1] "On the 'Blaze-currents' of the Crystalline Lens," *Proc. R. S.*, vol. 71, p. 184, 1902.

the lens. During the following year I tested the eyes of a good many fish in this way. For table purposes I became prejudiced in favour of fish on the crystalline lens of which I had previously found blaze-currents to be present. Nevertheless I did not go so far as to refuse to eat fish on which I had failed to find the reaction. It is not present in the lens of frozen fish, and since such fish may be perfectly good (or bad), the lens reaction is not a practical criterion to distinguish good from bad fish, although its presence is proof positive of good fish.

I am now studying the crystalline lens of mammalian eyes—of sheep, cats, and rabbits—more especially as regards the effect of high temperatures upon its blaze-currents. I am doing so partly from motives of pure curiosity, in order to learn how the lens, as compared with other tissues, is affected by heat, partly from a practical motive. We are informed that glass-workers are liable to a special kind of cataract that may (or may not) be due to heat-rays focussed in the lens. I do not know much about this matter now, nor whether my scientific curiosity is likely to lead to any useful practical result as regards glass-workers' cataract. But what I do know is that the application of my mind to questions as to the effects of heat upon the lens, and upon living matter in general, has taught me a good deal that I did not know before, and given me a chance of practising what I am very fond of preaching, *i. e.* that the ear-mark of the professing man of science should be, not that he is a learned man, but a learning man.

The effect of heat.—And now without apology or explanation let me open a parenthesis and devote the next few minutes to telling you what I have learned about the matter during the last year. I started at, or rather below, the zero line, in so far as the only fact known to me was

that nearly every text-book of Physiology contains the statement that nerve and muscle are excitable by electrical, mechanical, chemical, and *thermal* stimuli. I very soon found that as regards thermal stimuli this glib statement has no foundation in fact. All my attempts to stimulate nerve and muscle by means of sudden heat failed entirely. The question, "Do thermic shocks act as nerve-stimuli, or as muscle-stimuli?" received a clearly negative answer. Then I set to work to test the electrical effects of thermic shocks on nerve, on muscle, and on the skin, and then on vegetable tissues, and compared the effects in each case with the effect of true excitation. The results were quite remarkably clear and satisfactory, so much so, indeed, that they can be summed up in a sentence or two, or in a diagram helped out by a line or two of explanation. Here is the diagram (Fig. 44) and the summary, and what I believe to be the general conclusion to be drawn from all the data taken together.[1]

Let AB, Fig. 44, represent a muscle, or a nerve, or a piece of skin connected with a galvanometer by two points A and B; we shall follow out what takes place at B when that point is excited or injured and when it is heated. When the galvanometer spot moves to the left it indicates current in the tissue from B to A, and we call B negative (="zincative"); when it moves to the right we call B positive.

In the case of *Muscle*, we know that injury or excitation of B renders B negative, *i. e.* gives deflection to the left; and we find that thermic shocks *hhh* give deflections to

[1] "Do Thermic Shocks act as Nerve Stimuli?" *Proc. Physiol. Soc.*, Jan. 23, 1909. "Do Thermic Shocks act as Muscle Stimuli?" *Ibid.*, Feb. 27, 1909. "The Effect of Heat upon the Electrical State of Living Tissues," *Proc. Royal Soc. B.*, vol. 81, p. 303, 1909. But on the other side see Jensen in *Verworn's Zeitschrift*, vol. 9, p. 435, 1909.

the right, *i. e.* that they render B positive. We say, therefore, that the electrical effect of heat is in an anti-excitatory direction.

In the case of *Nerve*, we know that, as in the case of

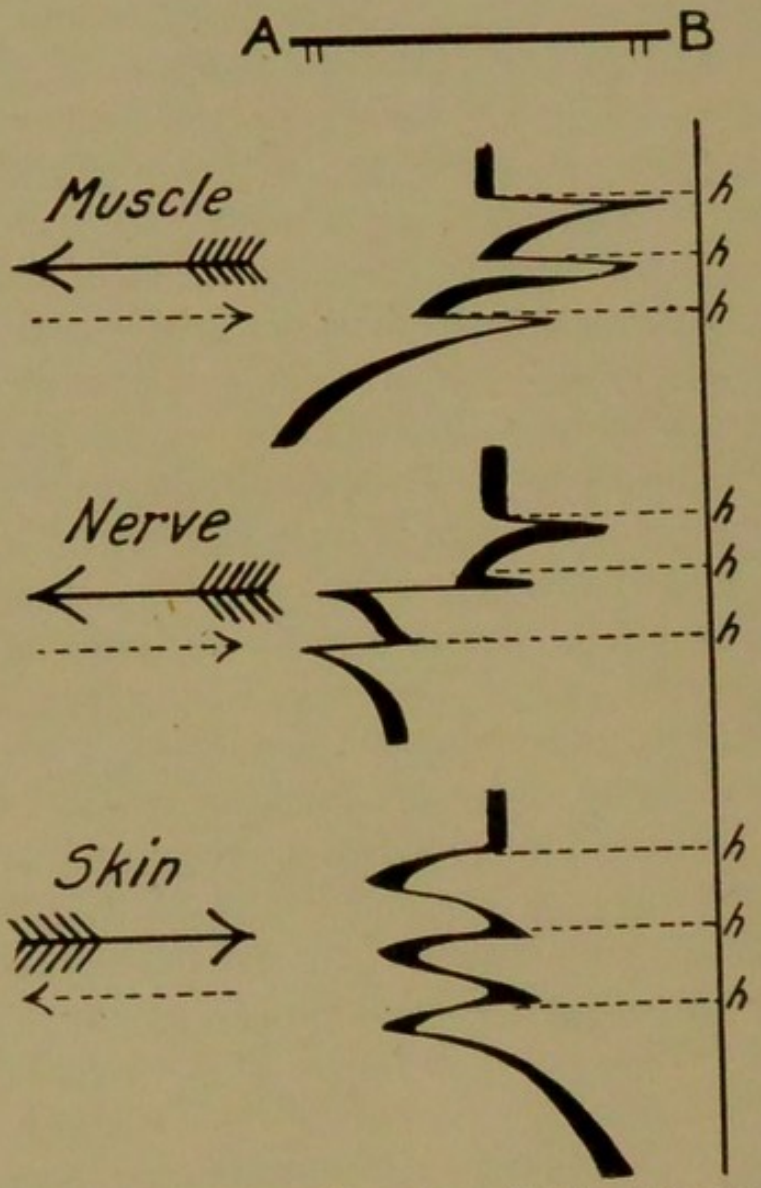


FIG. 44.—The tissue in each case is heated near B giving deflections as shown by the dotted arrow—opposite in direction to the effect of excitation of B, as shown by the full arrow.

Muscle, injury or excitation of B will give deflection to the left ; and we find that thermic shocks give deflections in the opposite direction. In this case, however, the deflection to the right is a rapidly diminishing effect ; although the thermic shocks have been very small, yet they have

been sufficient to develop injury as well as excitation, as shown by the deflection to the left following each deflection to the right. The true thermic deflection was, however, as before in an anti-excitatory direction.

The case of the *Skin* is peculiar. To bring out the galvanometric effects of excitation or of heat, our electrodes must be applied to the external and not to the internal surface. The effect at B of either mechanical or electrical excitation is current towards B in the skin, deflection to the right, *outgoing* through the skin at B, positive. The effect of thermic shocks is negative, deflection to the left. Thus as before we have it that the electrical change aroused by heat is of reverse sign to that aroused by excitation ; its direction is anti-excitatory.

And finally it may be mentioned, to complete the picture, that plants, preferably young shoots or stems, exhibit the same opposition between electrical effects of injury and of heat ; an injured spot is negative, a heated spot is positive.

Thus we have as a general conclusion, applicable to all these animal and vegetable tissues, that there is no such thing as thermic stimulation, and that *the electrical effect of sudden brief slight heat is in an anti-excitatory direction.* Heat is inhibitory, rather than excitatory, in relation to nerve and muscle.

How does this conclusion fall in with our other knowledge ? Well, I think it agrees with what we know about heat-paralysis.[1] I do not think it is inconsistent with the well-known fact that, within limits, chemical action is accelerated and retarded, at higher and lower temperatures respectively. And even if at this moment some unkind person should touch me with a red-hot poker, and

[1] Brecht, " Observations on the Nature of Heat-paralysis in Nervous Tissues," *American Journal of Physiology*, vol. xxii., Sept. 1, 1908.

ask whether I did not feel excited, I should not be persuaded of the error of my conclusion. For I know well enough that there are special nerve-endings in the skin that are excitable by heat, and others that are excitable by cold ; and in any case I shall not deny that excessive heat can produce injury of tissue, and that injury of tissue can excite pain.

Green leaves.—I mentioned green leaves at the beginning of this lecture in connection with the retina, as being likely to afford a natural sheet of living matter excitable by light, and responsive to the excitation by an electrical change, as the outward and immediately visible sign of chemical changes, which by other methods have been demonstrated as occurring under the influence of light. The question that I put to the leaf was answered in a day ; the questions to which the answer gave birth engrossed my attention for a year ; and the questions arising out of these questions would require time and trouble far beyond the means of a single observer, especially if his attention were distracted by other claims. Indeed, as far as I am concerned, I do not expect to be able to repeat what I did ten years ago, and give undivided attention to an observation extending over four successive days.[1]

But the nature of the subject, and the results so far obtained, can be explained more briefly. Perhaps the account of my first day's work will be the best means of sketching the subject to you ; after which a few representative records will serve the purpose of sampling its further progress and results.

[1] I then had the advantage of the assistance of Dr. L. Querton of Brussels, who subsequently (with my consent and concurrence) made use of these observations and records, accompanied by his own reflections and interpretation, in a Doctoral Thesis (" Contribution à l'étude du mode de production de l'Electricité dans les êtres vivants," *Thèse de Bruxelles*, 1902).

One fine morning, March 30, 1900, I went to the garden, with the idea of a "vegetable retina" in my mind, to pick out what might appear to be a promising leaf for the purpose in view. I fixed upon the leaf of *Iris Germanica* because it seemed to be in an active state, busy growing and building itself up from stuff stored in the bulb. The galvanometer, etc., stood ready for use in my study, and as the sun looked promising, I put up a heliostat on its stand to reflect some sunlight fairly steadily where it was wanted. Then I got a box and cut a hole in the top, over which a shutter and a vessel of water were arranged and through which sunlight was to be directed by a mirror fixed at a suitable angle. Unpolarisable electrodes were set up inside the box just under the hole; one of the electrodes B was surrounded by a flat shield of black paper, the other electrode A was left unshielded. The leaf was now put in place, and the two electrodes brought into contact with it, so that half the leaf in contact with B was covered by the shield, and the other half A was left unprotected. The box was closed, and the circuit between leaf and galvanometer through the electrodes was verified. The whole arrangement was left for a few minutes to settle down. Finally, all being well, sunlight was admitted through the hole in the box so as to fall upon the half-protected leaf, and therefore, *as shown at once by the effect on the galvanometer*, to arouse activity in that unprotected half. In this particular case—in which fortunately the deflection was photographed, so that I can to-day put in the lantern the actual answer given by that iris leaf nine years ago—the direction was such as to show that the first obvious effect of sunlight upon the leaf was to render the half thus excited galvanometrically negative (= "zincative"). Light gave rise to a current in the leaf from the excited to the unexcited half, just as the localised

excitation of a muscle or a nerve gives rise to a current from the excited to the unexcited part.

The rest of the day was spent in making sure that there was no mistake about the matter. The experiment was repeated, with and without a vessel of water placed over the hole to cut off heat-rays. No difference. While the light was on, the water vessel was slipped on and off. No effect. A hot poker was brought over the leaf, giving off

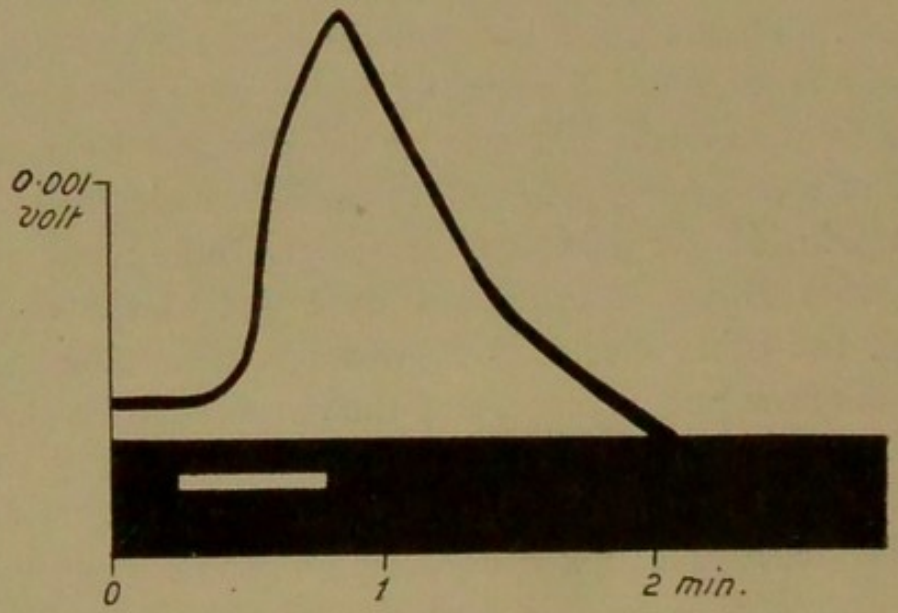


FIG. 45.—Electrical response to sunlight of a leaf of *Iris Germanica*. The white bar below indicates the time of exposure to sunlight.

plenty of heat but no light. No effect. Therefore the leaf had responded to light-rays, and not to heat-rays.

Apparatus was then improvised—I need not describe it—to give a signal of the instant when the leaf was exposed to light, so as to learn how long a time elapses before the leaf begins to respond to light. The time was thus found to be between two and three seconds. Finally the leaf was killed by immersion in hot water and tested again by exposure to light. No response. Therefore the previous response was a sign of life. The account of these results was written up in the evening, and com-

municated to the Société de Biologie, in Paris, in the course of the following afternoon.[1]

As for the rest, sunlight in London being a variable and capricious quantity, the first thing I did on my return was to arrange an arc-light in its stead. This answered quite as well as sunlight, and was of course much more convenient. During the month of May all sorts and conditions of leaves were brought up to the galvanometer for trial —iris, begonia and mathiola, tropæolum, ivy, horse-chestnut, hyacinth, and tobacco leaves. I soon found that leaves vary almost like people, and that when you know them you can classify them and set values on them. Their tempers seem to vary. Some leaves—ivy and horse-chestnut, for instance—are sluggish and sulky. They don't answer at all, so I left them alone. Others are lively and communicative, and it was delightful to sit and watch their behaviour according as their supply of carbonic acid was altered, or their vivacity modified by chloroform or ether or alcohol. Iris leaves were excellent, and I got to know them better than any other leaves—their differences of temper, in youth and in old age, in the morning, and at the end of a sunny day's work. I had been lucky in my first choice of a busy young iris leaf. Such a leaf, at its active time of life, gives a vigorous response amounting to upwards of 0·02 volt, whereas later, when the plant has put forth its flower, the leaf response fades and fails, as if the leaf's task in life had become accomplished.

If a botanist objects to this view and says that the leaf has *not* finished its task at this stage, and is busy storing up starch in the bulb for future use, I can only say that the matter requires further investigation. I have found the case to be as I have just described it to you—on *Iris*

[1] *Comptes Rendus de la Société de Biologie*, 31 Mars, p. 342, 1900.

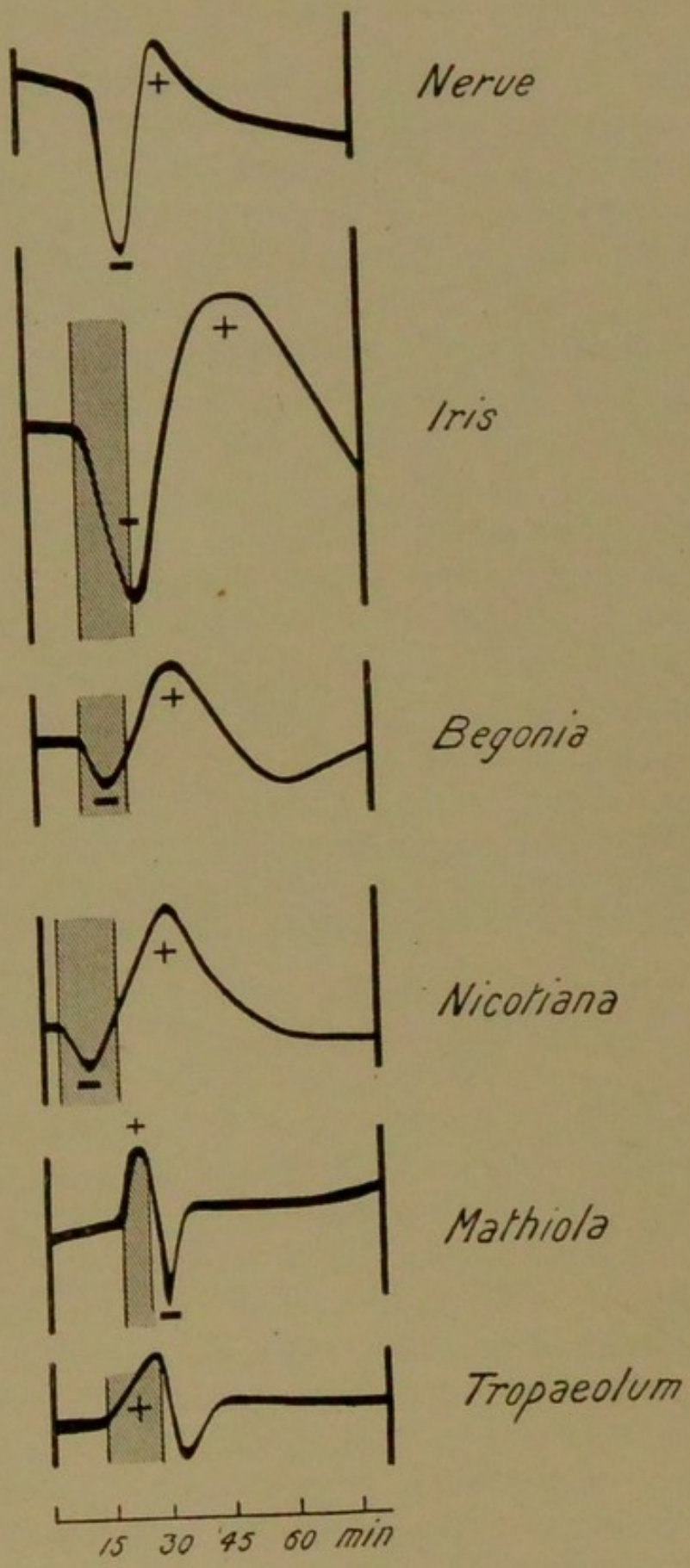


FIG. 46.—The electrical responses to light of various green leaves as compared with the normal response of nerve to electrical excitation. (The nerve response is on a different time-scale.)

Germanica, in two successive years, in 1900 and 1901—and I should be glad to be confirmed or corrected by any competent observer. My observations are nearly ten years old.

But it would be wearisome to listen to a farmer's description of his cattle unless one were oneself a farmer, and I do not wish to weary you with details. Still, just as the farmer might trot out his best beasts and perhaps tell his visitors the story of one of his most troublesome beasts, I shall show you the characteristic signatures of some of my best leaves, and tell you the story of a particularly troublesome one, over which I sat with intervals for a period of ninety-six hours. Bits of its story are illustrated by the long diagram above you, which represents episodes in the autobiography of my favourite plant, *Nicotiana*, of which you may see the normal signature among those of what I call my best plants (Fig. 46).

The tobacco-leaf in question, still attached to a vigorous plant enclosed in the dark box, was connected to a galvanometer by two electrodes, A and B, as previously described, and illuminated for five minutes at intervals by means of an electric arc. The position of the galvanometer spot was recorded on a series of photographic plates.

Summary of the Observation (June 19–23, 1900).

During the first five hours of observation with the leaf in normal air, the reponse to light was regularly of a value of 38 to 47 units (the "unit" being 0·0001 volt).

At the 20th hour the response was 38 units.

At the 22nd hour the leaf was submitted to the action of a current of expired air containing from 1 to 2 per cent. of CO_2. The response taken at quarter-hour intervals was 37, 74, 90, 70, 65—*i. e.* it was augmented.

In normal air 6 hours later it was 42.

At the 36th hour expired air (with tobacco-smoke) raised the response to 60.

At the 48th hour by a full stream of CO_2 from a Kipp's apparatus the response was completely abolished and remained so for 2 hours.

In normal air 21 hours later the response was regular at 50.

At the 70th hour the leaf was submitted to the action of ether vapour, which completely abolished the response. It did not return within the next two hours. But on the morning of the next day it was = 12, and did not augment during the subsequent 5 hours. The leaf was no longer vigorous and the observation was therefore terminated.

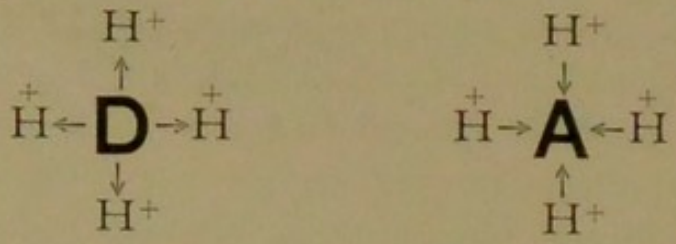
I lay stress upon the fact that the effect of CO_2 upon the leaf-response to sunlight is an augmentation by a moderate amount of CO_2 and suppression by a large amount of CO_2.

Let me recall your attention for a moment to the collection of leaf signatures in Fig. 46, in comparison with the typical response of nerve to electrical excitation—viz. negative followed by positive movement. The response of *Iris* to luminous excitation is of a very similar character only more prolonged—negative during illumination, positive after illumination. In that of *Begonia*, and more so in that of *Nicotiana*, the initial negative change gives way to positive even during illumination. With *Mathiola* and *Tropæolum* the response is positive from the outset of illumination. In fact, all the varieties of negative and positive response that we have witnessed in the case of nerve have repeated themselves on a different scale of time with green leaves. In the case of nerve we found it necessary to postulate, though we could not prove, the existence of two opposed chemical movements. In the case of the retina the existence of two opposed electrical movements was distinctly recognised, but we could not see any possible way of inquiring into the actual chemical origin of these movements. In green leaves we again have evidence of a double electrical movement, and we

are definitely acquainted with the existence of two opposed chemical movements—the analytic process of respiration of which CO_2 is the principal outcome, and the synthetic process of assimilation of which CO_2 is the principal income. We may be allowed to hope that at some future time the conditions of existence of these two functions may become better known to us through the systematic study of their electrical signs in connection with the chemical changes that are known to take place in vegetable protoplasm under the influence of chlorophyl. We know that photosynthesis culminates in the formation of sugar and starch, and that formaldehyde, H.CHO, is in all probability an early station on this up line. It is permissible to imagine that in such synthesis there is an electrical change opposed in direction to that which occurs in the dissociation of sugar into carbonic acid and water. If at any centre of dissociation, characterised by acidification, the electrical movement is centrifugal, in what we have designated as the negative direction, then at any centre of association, characterised by deacidification, the electrical movement should be centripetal, *i. e.* in the positive direction. Pictured in terms of ionic movements, the product of dissociation, carbonic acid, consisting of the ions $\overset{+}{H}$ and $\overset{-}{HCO_3}$, in which the velocity of $\overset{+}{H}$ exceeds that of $\overset{-}{HCO_3}$, gives current *from* the focus of dissociation—*i. e.* in the centrifugal direction, *i. e.* active protoplasm is zincative or negative in relation to resting protoplasm. Whereas a product of association—formaldehyde let us say—during its formation, gives rise to a current in the opposite direction, *i. e.* centripetal towards the focus of synthesis, as contributory to which we must reckon the electropositive ion $\overset{+}{H}$.

Our conception thus takes the simple form that current

is centrifugal from any point of dissociation, centripetal from any point of association, thus :—



The more prominent of the two electrical effects is the centrifugal current of action. This is quite intelligible when we consider that ingoing active oxygen Ō whether during or after dissociation must be the vehicle of centrifugal current—*i. e. with* the **D** current, against the **A** current.

Flower petals give no electrical response to light, although if we remember how many of them are heliotropic we might perhaps expect some such sign of an excitatory action of light. But so far I find that the *sine qua non* of a clearly marked photo-electrical response is the presence of living cells, containing chlorophyl. But a living flower petal should be, and as a matter of fact is, able to respond affirmatively to the question, "Are you alive?" by the more general answer to which I have given the name of "blaze-current." When I first tried this on a flower—a white lily as it happened—I soon found that it was a very tender thing, easily "shocked" and exhausted by the test, so that the response rapidly grew fainter and died away altogether with repetition of the test. That gave me a lead. The flower had evidently been "shocked to death"—"electrocuted," and "electrocution" by sufficiently strong shocks might, in any case where it was desirable to make sure, be expected to afford a convenient means of killing or stunning a subject of experiment, without disturbing its contact with the electrodes, far more convenient therefore than killing by scald-

ing. And so I was led up to what I alluded to a little while ago as "the experiment of the electrocuted lily."

I do not intend to repeat that experiment to-day—or, rather, I intend to do so in a somewhat modified form—which I might call—as I shall certainly remember it—"the experiment of the Californian apple."

Thinking about the subject-matter of to-day's lecture, I

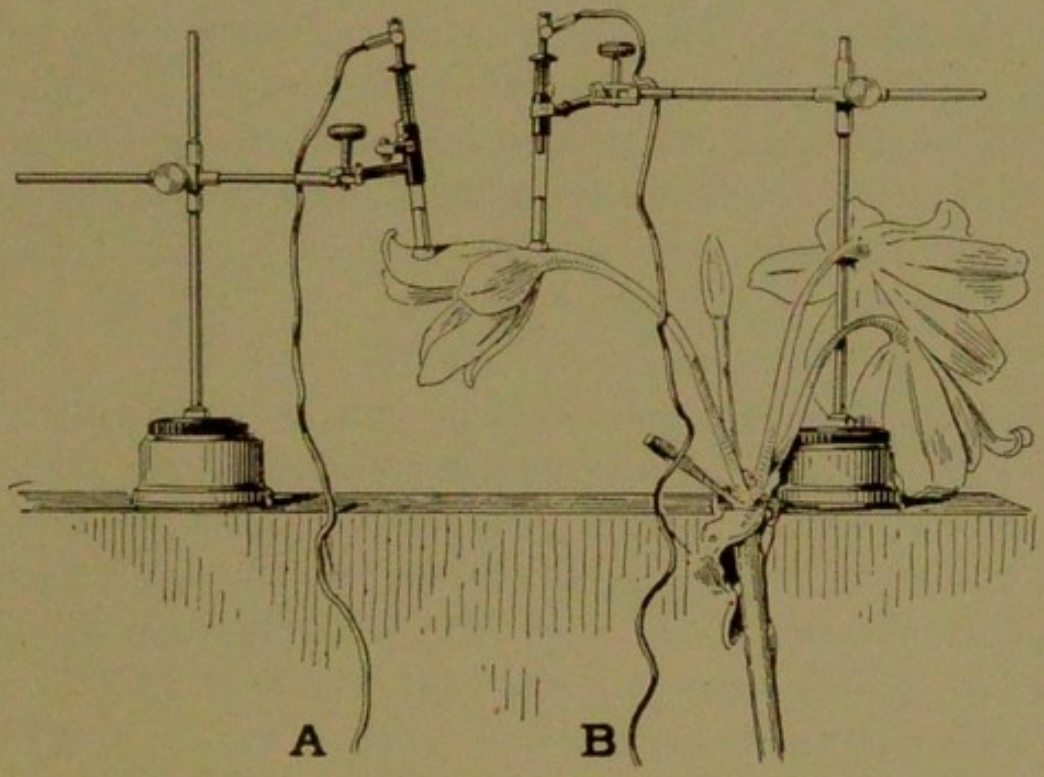


FIG. 47.—THE ELECTROCUTED LILY. The electric shocks used for excitation and for electrocution pass *to* the flower by the wires A and B and the electrodes in contact with it. The subsequent response or blaze-current passes *from* the flower by the same electrodes and wires to a galvanometer not shown in the figure.

The experiment has three stages :—

1. Excitation gives a large response, *i. e.* the flower is alive.
2. The flower is "electrocuted" by a strong electrical current, *i. e.* it is killed or stunned.
3. Excitation now gives little or no response.

(In the actual lecture experiment, as stated in the text, an apple was substituted for the lily flower.)

picked up these two apples. They are, as you see, of equal size, but one is green and the other yellow ; the first is young and unripe, the other is ripe. Both are of course alive, as we shall see by the blaze-test which I am now about to apply to them. The two responses are

unequal ; that of the young apple, as far as may be judged in a brief lecture-experiment, is about twice as great as that of the old apple ; both responses are indeed no more than skin-deep. I now submit both apples to the ordeal of electrocution—comparatively gentle electrocution, however, because I do not want to shock them to death, but only to stun them, so to speak, in order to obtain a *temporary* abolition of the blaze-current. Then I repeat the blaze-test, to which, as you see, there is no response in either case ; both apples have been stunned (or killed, perhaps). But I shall leave them alone for half-an-hour, and if I have been lucky, they will begin to respond again by and by, and probably the young apple will get well sooner than the old apple.[1]

Do you understand? Are not these dry details, about leaves and flowers and fruits, charged with meaning to us? Do you not want to know more about the machinery, if not the ultimate meaning of life?—*how* living things work, and *how much* they work—in default or in expectation of the *why* and wherefore of the Life of which we form part? But we must pass on.

That blaze-currents are a *measure* as well as a *sign* of life—that they tell us "how much" things live, as well as whether they are alive or dead—is well illustrated, I think, by the following series of numbers, representing values in fractions of a volt, of the responses given by a series of seeds (Phaseolus) 1 to 5 years old.[2]

At	1	2	3	4	5	years old
the average blaze was =	0·0170	0·0052	0·0043	0·0036	0·0014	volt.

As you probably know already, seeds deteriorate with keeping, and their loss of value can be gauged by finding how many seeds per cent. of a given sample germinate

[1] Note 6, Appendix.

[2] "On the Vitality of Seeds Tested by an Electrical Method," *Proc. Royal Soc.*, vol. 68, p. 79, 1901.

properly under ordinary conditions of temperature and moisture. Professor Johnson of the Royal College of Science, Dublin, who has applied this test on a larger scale than I have, and to much smaller seeds than I had imagined possible, tells me that the test is valuable not only by reason of the time it saves, but also by reason of its reliability ; to report on a seed sample by the germination test takes ten to thirty days, whereas by this method the seeds only require a day or two before the test can be applied.

If I were a seed-merchant, I should put up the dollars to send a capable young man or woman to this laboratory to learn this test, and I should expect to add to the dollar value of my business in due time. But, again, we must pass on.

I want, in conclusion, just to mention one more experiment. You remember about the cat's-pad experiment shown in a previous lecture (p. 24). I have spent a good deal of time in trying whether it could be reproduced on the human subject, by exciting accessible nerves like the median and ulnar or the peroneal nerve, and leading off from the skin of the hand or foot. The results have so far been dubious, but I must try again when I get home. On the other hand, the effects of direct excitation of a piece of skin, taken from an amputated limb, or from the post-mortem room, have been altogether satisfactory.[1] The skin of a man goes on living for two or three days after his death. In the case of a seed the blaze-current is the first sign of life ; in the case of the skin it is literally the last sign of life. There could be no question of suspended animation or trance, if it was found that a portion of the skin did not give any blaze-current.

[1] "On Skin Currents." Part III. "The Human Skin," *Proceedings of the Royal Society*, vol. 70, p. 374, 1902. The longest period after death at which I have found the skin to be still alive has been ten days.

Addendum.—This lecture is finished; but those among you who can stay a little longer may be interested to watch an experiment that belongs properly to to-morrow's lecture, but that would, I fear, take too much time, as it is one that I am not yet very familiar with. Professor Loeb has to-day shown me some of his own experiments on Daphnia, and has been good enough to let me use some of his material for a different sort of trial of what I spoke about in my first lecture, and shall allude to again to-morrow, viz. the action of anæsthetics. I have spent some hours to-day in looking at little groups of Daphnia in watch-glasses to which I added various amounts of chloroform and ether and alcohol. I wanted to see whether the scale of equivalence determined by the effects of these reagents upon muscle would hold good for their action upon these little organisms. As far as I was able to judge from the observations to be made in such a short time, the scale holds good, but the series of concentrations used for muscle is too high for the purposes of a rapid demonstration of the *temporary* character of the effects, though they answer very well to show in lecture the simple fact that the three anæsthetics at these comparatively low concentrations do very rapidly send the little animals to sleep—or at least put a stop to their active movements. The watch-glass now projected on the screen contains Daphnia, swimming about in all directions, that were profoundly anæsthetised and immobile two hours ago, in consequence of the addition to the water of about one-tenth of its volume of a centimolecular solution of chloroform. Now they are as lively as ever they were. Let us add a little chloroform solution and watch them come to rest again during the next minute or two.

Ether in decimolecular solution, and alcohol in molecular solution, produce very similar effects. The

alcohol watch-glass full of intoxicated Daphnia—"dead-drunk," in fact—would be just the thing for a temperance lecture, and in that case it would not be necessary to show any recovery from the effect. But, seriously, of course it goes without saying that arrest of movement does not show that alcohol *is* a bad thing, any more than recovery of movement would show that alcohol is *not* a bad thing. Our opinions about alcohol must be formed quite otherwise than by experiments of this type. Our business to-day has simply been to compare the toxic power of alcohol with the toxic power of ether and of chloroform. As you have seen (p. 9), alcohol is a very weak poison—the weakest on my list—more than 10,000 times less poisonous than aconitine, which heads the list. So that the danger of excess consists, not in the fact that alcohol is a powerful poison, but rather in that it is a relatively weak poison, of which even considerable quantities may be absorbed with impunity. Here is a list of some drugs used in medicine, or present in articles in daily use, such as tea, coffee, and tobacco, arranged in order of their molecular toxicity as tested upon muscle[1]:—

Aconitine	1000
Quinine	100
Nicotine	33
Theobromine . . .	18
Caffeine	12
Chloroform	6
Ether	0·72
Alcohol	0·06

To estimate the relative toxicity of a glass of beer and of a cup of tea, we must of course take into account the relative amounts of the respective "poisons" in these

[1] A fuller list is given in the Appendix, note 1.

beverages. Dr. Veley and I have done so for coffee, tea, wines, whiskies, and beers, and have compared their relative toxicities upon muscle. You may be interested to hear that the toxicity, in relation to muscle, of a cup of coffee (made in the laboratory with saline solution) is approximately equal to that of a glass of beer. The coffee contained about 0·1 per 100 of caffeine, the beer contained between 4 and 5 per 100 of alcohol.

Plants, like animals, can be anæsthetised. Their visible movements, where such exist, and in any case the invisible chemical movements of which the outward and visible signs are electrical changes, are arrested, temporarily or permanently, by ether or chloroform vapours. Several years ago, when we knew less about these things than we do now, Professor Farmer and I set ourselves to compare the effect of carbonic acid, of ether, and of chloroform upon samples of vegetable and of animal protoplasm. We took as our examples the cells of *Elodea canadensis* and the nerves of *Rana temporaria*, and we observed simultaneously (1) under the microscope the processional movements of the chlorophyl bodies round a cell and (2) on the galvanometer the electrical responses of a nerve, before, during, and after both objects had been simultaneously submitted to the same current of carbonic acid, or of ether vapour, or of chloroform vapour.[1] The results are given in graphic form on this diagram (Fig. 48), and as you see the effect of the three reagents were similar in the two cases. In both vegetable and animal the immobilisation by strong ether vapour was temporary, while by strong chloroform vapour it was permanent; both objects were killed.

[1] "On the Action of Anæsthetics on Animal and Vegetable Protoplasm," *Proc. Royal Soc.*, vol. 63, p. 213, 1898.

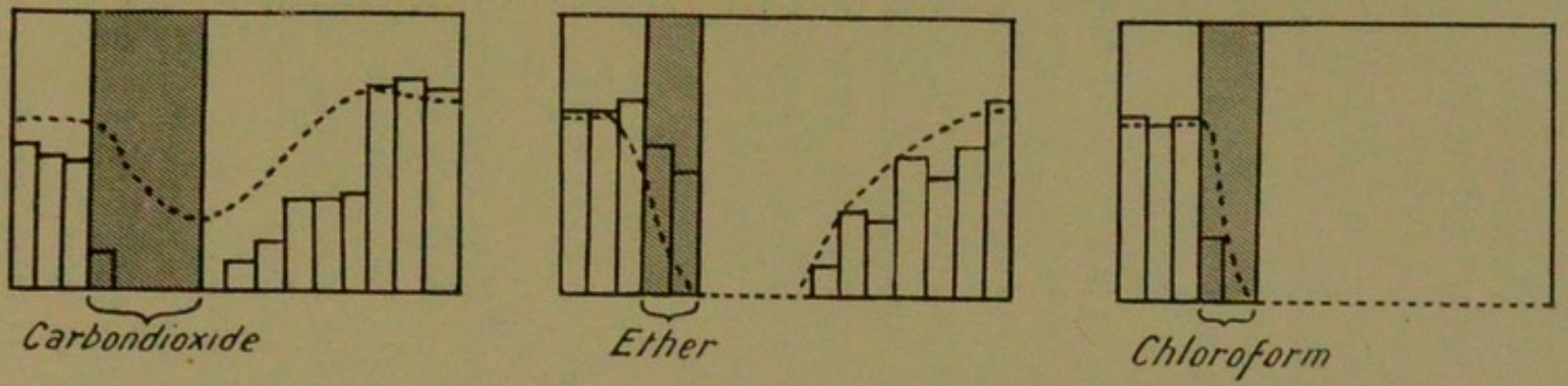


FIG. 48.—The action of carbon dioxide, of ether and of chloroform upon the circulatory movement in the cells of Elodea Canadensis. The heights of the columns indicate rate of movement at successive minutes before, during, and after action of the vapour, which is shown on the figures by the vertical dark bar. (The alterations of excitability of an isolated nerve by the same reagents was simultaneously observed, and are indicated by the dotted lines.)

LECTURE V

BEFORE the discovery of anæsthesia by the inhalation of ether vapour (by Wells and Morton in 1846) and of chloroform vapour (by Simpson in 1847), the only alleviation we could have hoped for during a surgical operation would have been the imperfect deadening of pain to be procured by swallowing as much brandy as possible, so as to get into the blood something approaching an anæsthetic quantity of alcohol ; otherwise stated by getting as intoxicated as possible. And we must reckon the discovery of the more powerful intoxicants, ether and chloroform, as having conferred upon us one of the clearest and most welcome benefits ever conferred by man upon mankind, since not only has it made possible the achievements of unhurried surgery, but above all it has taken away from every one of us in imagination as well as in fact the nightmare of unavoidable and unendurable torture.

A drachm of chloroform is physiologically equivalent to 15 drachms of ether or nearly 2 fluid ounces. Experience proves that ether is above all the safe anæsthetic, chloroform the powerful anæsthetic. Alcohol, of which 75 drachms, or nearly 10 fluid ounces, are the equivalent of a drachm of chloroform, cannot be inhaled, or even swallowed, in amount sufficient to ensure complete anæsthesia. Yet theoretically a pint of good brandy or whisky, which would contain over 300 c.c. of alcohol, should be at least as effective as a teaspoonful of chloroform, *i. e.* about 4 c.c.

The two vapours, ether and chloroform, have practically

held the field of anæsthesia for the last sixty years. In some hospitals, such as the Massachusetts General Hospital at Boston, ether is the anæsthetic exclusively employed. In others, such as the Edinburgh Royal Infirmary, chloroform is the regular anæsthetic. In the British Empire generally, chloroform predominates. On the American side, ether. In Europe the field is disputed between ether and chloroform. And various authorities swear by various mixtures of ether and chloroform, or of alcohol, ether, and chloroform. The medical partisans of ether urge the all-sufficiency of ether and the danger of chloroform. The medical partisans of chloroform minimise the danger of chloroform, and point to the inconvenience of ether, and to the serious after-effects that they believe to result from its use.

What are we to think, and what shall we do ? Should we take chloroform or ether for ourselves and for our children ? That is the most cogent form in which the question can present itself to us, and most of us may expect one day to have to answer it. The answer carries with it our answer to the question whether we should give chloroform or ether to other people.

My answer to the question couched in this its most searching form, is as follows :—

If I had to undergo anæsthesia unexpectedly at the hands of an unknown administrator, I should take ether. If I had to undergo anæsthesia after due warning, I should take chloroform, but only at the hands of an administrator of known skill and experience, with or without the assistance of apparatus by which the concentration of chloroform vapour could be controlled. I should much prefer such apparatus to be used, but I should not wish the administrator to be hampered by having to use apparatus with which he was not familiar.

Viewing the matter from the more general and impersonal standpoint, I should, in the present state of matters, advise the choice of ether as the ordinary routine anæsthetic for the administrator who has not the time or inclination to observe the precautions or the mechanical refinements by which the administration of chloroform can best be made "safe." I shall discuss such precautions and refinements later.

The chief reason why, in spite of the early teaching of Snow in 1858 and of Paul Bert in 1870, the practice of chloroform administration has not been as "safe" as it might have been, is that chloroform and ether have been, so to speak, bracketed together, and treated as being very much on the same footing, the former being indeed recognised as the more powerful and the more convenient, but both reagents being administered by similar methods, *i. e.* by causing the patient to inhale vapour from a liquid poured more or less copiously over a towel or mask applied more or less closely over the face. More care and caution were as a rule observed with chloroform than with ether, and as an outcome of experience it became customary to recommend that chloroform should be administered by "an open method," ether by "a closed method," *i. e.* that the former required greater dilution by air than the latter reagent. But the instantly dangerous augmentation of percentage that can occur with chloroform, when the mask or towel is closely applied to the face, either to accelerate induction, or through simple inadvertence, for however short a time, during perhaps no more than two or three deep inspirations, has never been sufficiently realised. Under such conditions accidents have occurred and are likely to occur again. One deep inspiration of, say, 2000 c.c. of air at, say, 5 per cent. of chloroform vapour, conveys into the lungs 100 c.c. of

chloroform vapour, and thence into the pulmonary blood (already more or less charged with chloroform) something like 50 c.c. of chloroform vapour. Two or three deep inspirations of this sort will at once overcharge the blood with chloroform, and this overcharged blood may at once arrest the action of the heart. And a heart arrested under these conditions, overloaded with blood which is overcharged with chloroform, is not likely to beat again. That is what I believe to be the ordinary mechanism of sudden death by cardiac syncope.

The margin between anæsthesia and death is relatively narrow for chloroform, because chloroform is a most powerful drug, with which therefore it is easy to overcharge the blood.

The margin between anæsthesia and death is relatively broad for ether, because ether is a less powerful drug, with which therefore it is difficult to overcharge the blood.

This is not to say that we should reject chloroform anæsthesia in favour of ether anæsthesia, but that we should adopt means for the properly graduated administration of chloroform. And by properly graduated administration I mean the *continuous administration of chloroform vapour and air between the limits of* 1 *and* 2 *per* 100.

I am not making this recommendation for the first time. It was the principal conclusion of my address to the section of Anatomy and Physiology of the British Medical Association at Montreal in 1897, and of my communication to the Society of Anæsthetists in London in the following year. It is—as far as I am concerned—the principal motive of a report presented at the recent meeting of the British Association at Winnipeg.

My judgment of the matter as it stood twelve years ago has only been confirmed by what I have learned since then. But whereas in 1897 I could not go beyond

the recommendation of the 1 to 2 per 100 limit, to-day I can offer, and demonstrate on the lecture table, simple means of measuring the percentage of chloroform in air, and of securing in the operating theatre known percentages, visible during the operation to operator and administrator, and to all whom it might concern.

You will understand the principle of the method at once from a very simple experiment.

There are at present in the two scale-pans of this balance two similar glass bulbs exactly counterpoised. Each bulb has a capacity of 250 c.c. and contains air. I pass through one of the bulbs a stream of air that has passed over chloroform, and that contains therefore a certain amount of chloroform vapour. How much? I close the bulb and replace it on the scale-pan. It is heavier. I re-establish the counterpoise. The weight required for this purpose is 35 milligrammes, *i.e.* the percentage of chloroform is 3·5.

Not a very difficult performance is it?—in fact I think it would be difficult to find anything else quite as easy in the quantitative estimations of the laboratory. But I should be ashamed to say how long it took me to find this simple way out of a real difficulty.

The arithmetical data upon which the result depends are as follows—

1000 c.c. of chloroform vapour weigh		5·3	grammes
1000 c.c. of air weigh . . .		1·3	,,
Difference per	1000 c.c. =	4·0	,,
,, ,,	1 ,, =	4·0	milligrammes
,, ,,	2·5 ,, =	10·0	,,

So that 1 per 100 of chloroform vapour in a 250 c.c. bulb is indicated by a weight difference of 10 milli-

grammes, and therefore 3·5 per 100 is indicated by 35 milligrammes.

This answers all practical purposes; you need not be troubled with temperature and pressure corrections. Probably any one who wants these corrections knows how to apply them.[1]

The next step, by which I sought to obtain for the laboratory a means of estimating from moment to moment, and recording, the fluctuations of percentage taking place in the chloroform-and-air mixture delivered to an animal, and of varying the percentage as desired for experiment, put me in possession of an instrument that at once fulfilled its laboratory purpose, and at the same time is obviously capable of being transferred to the hospital.

Instead of weighing in air a bulb full of chloroform mixture, I weighed, or rather counterpoised, a closed bulb full of air, floating in a vessel traversed by the chloroform mixture; the bulb, of course, rose and fell as the mixture was rendered more or less dense by more or less chloroform vapour. The pointer of the balance was then graduated in chloroform percentages by appropriate weights—40, 80, and 120 milligrammes for a litre bulb floating in 1, 2, and 3 per cent. of chloroform and air. A light pen fixed to the beam of the balance, and a smoked cylinder, served to give a record of the rise and fall of the bulb with rise and fall of the chloroform percentage, and incidentally served the useful purpose of damping the oscillations of the beam and pointer. In order to avoid accidental fluctuations of the percentage delivered to the animal, it was advisable to use a vessel of considerable volume, containing the mixture on its way to the animal. I used the case of the balance for this purpose. Air was pumped into it through or over the surface of liquid

[1] Note 7, Appendix.

chloroform, by the ordinary respiration pump, or by a bellows, and the mixture went out through a delivery tube to the tracheal cannula or mask. The large capacity of the balance case—in this case 30 litres—proved to be suitable for the induction of anæsthesia, and for its safe gradual modification. The chloroform percentage rose from zero to 2 per cent. in about two minutes; the lag of any desired diminution and increase of percentage, was about ten seconds; the pointer could at will be kept steady at any desired percentage. Finally, I may remark that for all ordinary purposes of the laboratory a comparatively coarse balance is best adapted; in the apparatus now in daily use in my workroom, the graduation is from 1 to 3 per 100, and the corresponding records have amplitudes of 6, 12, and 18 millimetres.

Judging from the comments of visitors to the University of London, acquainted with the various haphazard methods in use for producing and maintaining anæsthesia of the human subject—witnessing for the first time the ordinary procedure followed in the physiological laboratory for the induction and maintenance of anæsthesia in animals—experiencing perhaps for themselves what 1 per 100 of chloroform-and-air really is—the usual thought aroused seems to be one of regret that the human subject cannot be anæsthetised with equal uniformity and safety.

My own feeling is one of intense surprise that the clear practical experience of the laboratory should be so slowly realised by the medical profession, and that year by year the death-roll of chloroform anæsthesia should continue undiminished.

This (Fig. 49) is the diagram I used twelve years ago at Montreal, setting out as nearly as I could ascertain the yearly deaths *by* or *during* chloroform anæsthesia in England for the previous ten years. I then expressed

the hope that with our increasing knowledge this death-rate might be decreased.

It has not decreased. This (Fig. 50) is a more complete diagram, embracing a period of forty-four years from 1863 to 1907, constructed from the Registrar-General's returns. The numbers are for anæsthetics altogether, but as a matter of fact the numbers are almost entirely of chloroform deaths, deaths by any other anæsthetics forming only a small fraction of the total numbers. I have made out as accurately as was possible

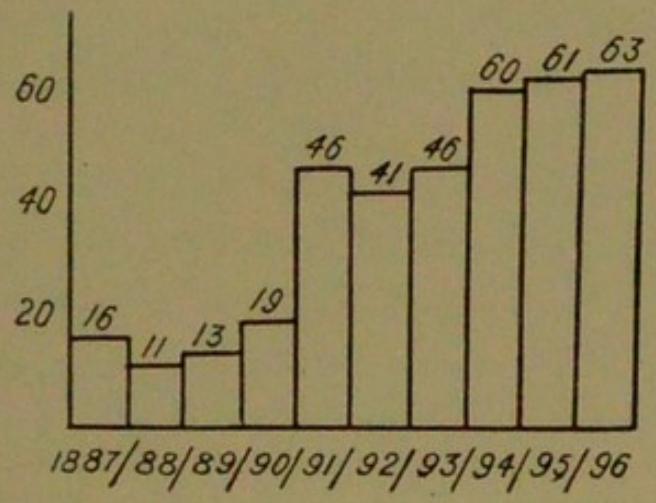


FIG. 49.—Deaths by chloroform in England and Wales during the years 1887 to 1896.

the numbers of deaths with chloroform alone for the last twenty years. They are indicated on this second diagram by the shaded columns.

Statistics, like any other data, may be more or less correctly taken or selected, and they do not always warrant the conclusions that are drawn from them. In any case, their origin has to be scrutinised. The figures given in the annual returns of the Registrar-General are derived from the reports of cases in which inquests into the cause of death have been held, and from medical certificates of the cause of death. It has been objected that these

returns must include many deaths *during* but not necessarily *by* the anæsthesia. That may be granted at once, but surely the defect is more than counterbalanced

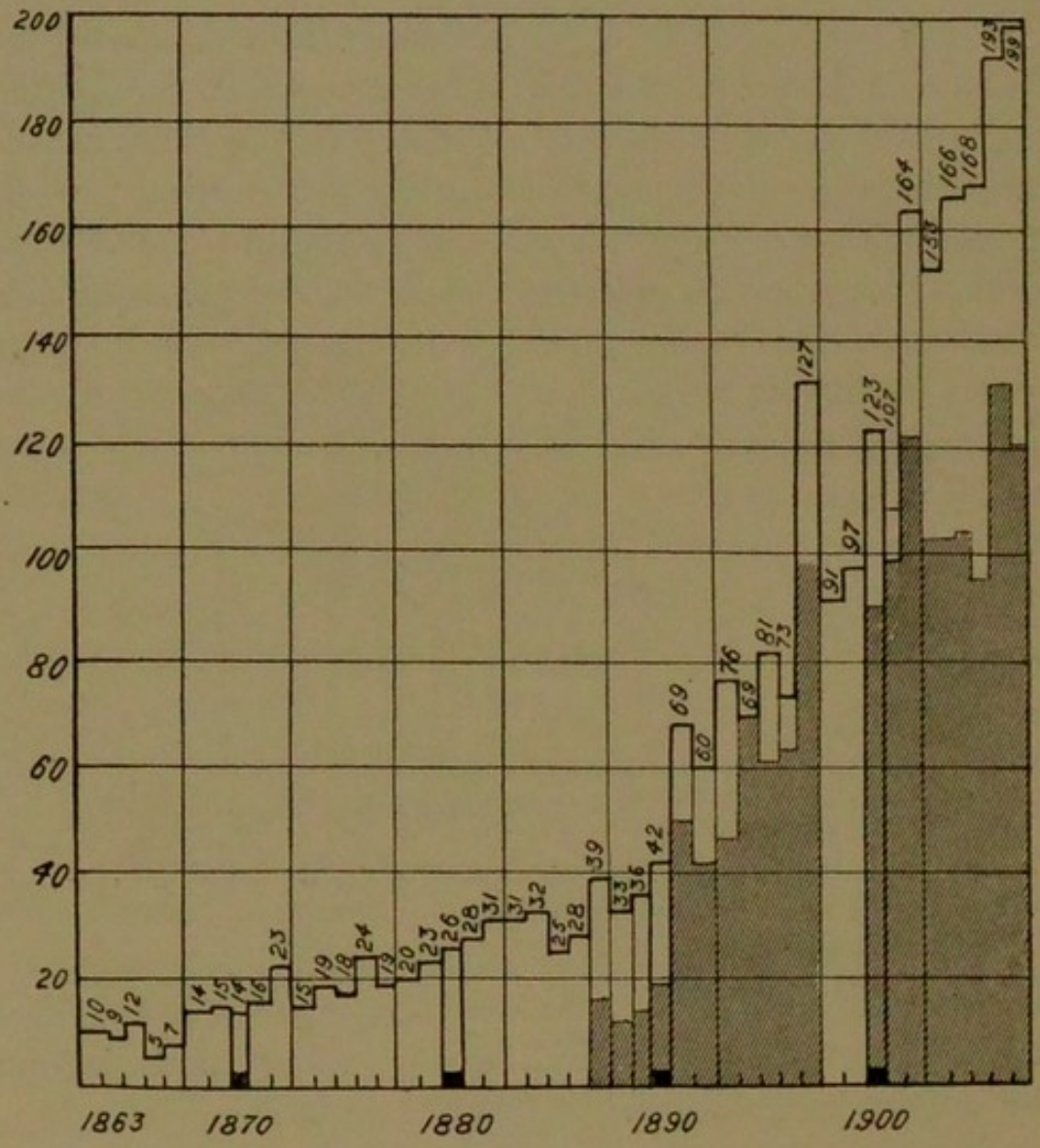


FIG. 50.—Diagram of the annual number of deaths registered in England and Wales as due to anæsthetics in the years 1863—1908. (The numbers of deaths due to chloroform alone from 1887 are indicated by shaded columns, with the exception of the years 1898–9.) The number of deaths officially returned for 1908 is 235.

by cases where the certificate makes no mention of an anæsthetic, and names some other "cause of death" if possible. Even a cursory examination of the medical literature of the last twenty years brings into evidence

that the spontaneous reports by medical men of accidents—especially of chloroform accidents—has markedly decreased. Taking, for instance, our two leading medical papers, the *Lancet* and the *British Medical Journal*, we find for the eight years 1893 to 1900 in the *Lancet* 148 reports, in the *British Medical Journal* 131 reports, and for the eight years 1901 to 1908 in the *Lancet* 18 reports, in the *British Medical Journal* 20 reports. To conclude from these confessedly fragmentary figures that accidents have diminished would obviously be absurd in presence of the imperfect but automatic returns of the Registrar-General. All that the medical papers show is that the number of reports has diminished. And when we examine the medical papers more closely this tendency towards diminution rather than increase becomes even more apparent. We find cases reported in which the context shows that chloroform must at least have been a contributory cause of death, under titles giving no clue to any such possibility, and removing them therefore from possible inclusion in the list of chloroform accidents.

It has been urged, in mitigation of these numbers of deaths, that the number of surgical operations, and therefore of cases of anæsthesia has greatly increased of late years. This is doubtless true, and it accounts for some of the increase in the number of deaths—how much, however, it is impossible to say, in the absence of any estimate of operation-frequency. But we can hardly admit that, *e. g.*, the number of surgical operations has doubled in the last ten years, while we find that in the same period the number of deaths has more than doubled. These numbers for the three periods 1878–87, 1888–97, 1898–1907, are 283, 666, and 1461.

So much for statistics. All that I have wished to

prove to you by these remarks is that, imperfect as are the statistics, they establish the fact that the administration of chloroform, as ordinarily practised, is attended with considerable danger.

And I state again here, what I have stated elsewhere on many previous occasions, that the danger is in large measure avoidable by a proper method of administration.

I shall describe and demonstrate one such method of administration, but before doing so I should like to say that I realise very fully that different methods are "proper" under different conditions, and that in circumstances of emergency any method can be a "proper" method, even that worst and most dangerous proceeding in which the surgeon is obliged to anæsthetise and operate single-handed, or assisted it may be by some quite untrained person. But if it may be proper under stress of circumstances to carry out a difficult surgical operation under the worst possible conditions, it would certainly be improper to do so under bad conditions when good conditions can be secured. The operation of anæsthesia ought to be placed on precisely the same footing. It should not be allowable to conduct anæsthesia under bad conditions when good conditions can be secured. And pray do not object that the habit of demanding good conditions unfits a man for dealing with similar duties under bad conditions. It does not; and especially not in the case of anæsthesia by chloroform, where the ability to deal with bad conditions is a direct consequence of knowledge acquired under the best possible conditions in the Hospital and in the Laboratory. I am convinced that a previous familiarity with the principles and use of apparatus for the administration of chloroform, so far from preventing a man from making good use in an emergency of a folded towel and a bottle of chloroform, will materially

increase his ability to do this in the best and safest way possible in difficult circumstances.

This is a very different matter from the routine use of a rough-and-ready method without due appreciation of its physical conditions. It fortunately happens that the percentage of chloroform and air breathed from a mask or towel at a suitable distance from the face, is a moderate one —not far removed from what we have learned to be the right percentage wanted for continuous administration—it is at something like 2 per cent., and falls or rises according as the mask is less or more closely applied, with consequently lower or higher values, according as the administration is less or more interrupted, while continuous anæsthesia is maintained. But it requires natural skill and no little experience, to anæsthetise well and safely by this method. The old rule of chloroform administration taught in the Edinburgh school, "*Plenty of chloroform and plenty of air*," brings about very much the same sort of percentage. Obviously the volume of chloroform and air mixture offered to inspiration is greater, and the administration more uniform, than if the chloroform is used in more niggling and irregular manner. And so it has happened that large numbers of cases of chloroform anæsthesia have been safely conducted in Edinburgh.

It is an extremely dangerous practice for any man—even the most skilful—to anæsthetise and to operate single-handed. Anæsthesia of even moderate uniformity cannot be secured under such conditions ; the continuous anæsthesia of the patient is necessarily the result of discontinuous waves of vapour—alternations of excesses and deficiencies of flow—not to speak of the interrupted attention of the operator. Granted that an emergency may arise where such a proceeding *must* be adopted, just as it can happen that a major surgical operation may be

required at short notice under unfavourable conditions. That does not signify that under ordinary conditions any reasonable precaution and safeguard may be neglected. Indeed, in this connection I shall repeat what I said a moment ago. Chloroform anæsthesia is in itself an operation of such gravity that it should in itself, apart from any surgical proceeding, be regarded and treated as a major operation, independently of the degree of gravity of the surgical element, and surrounded on its own account by every possible precaution and safeguard.

If this serious attitude towards chloroform is desirable within the medical profession—if it is accepted and declared to be unduly hazardous for a qualified medical man to anæsthetise and operate single-handed without necessity, how much more hazardous must we reckon it to be for non-medical men to undertake the double task? Should, for example, dentists in general, however skilful and experienced, be permitted to do so? I think not.[1]

Let me now describe to you our ordinary daily procedure in the production of anæsthesia by chloroform, as practised on animals in the Physiological Laboratory of the University of London.

First step.—The animal is placed in a closed glass chamber (a large bell-jar or a small cupboard with a plate-glass front) into which chloroform-and-air of desired percentage is pumped. The mixture is provided by a current of air driven through a wide-mouthed bottle containing liquid chloroform, into a large mixing chamber (capacity = about 30 litres) containing the chloroform balance, and provided with an inlet from the chloroform bottle, and an outlet to the animal chamber. The percentage of the mixture administered is indicated by the

[1] Note 8, Appendix.

pointer and scale. It is regulated by varying the depth of a tube in the chloroform bottle, and by admitting more or less air to the mixing chamber. In general, anæsthesia is induced by chloroform and air at 2 per cent., and the animal is kept under anæsthesia at 1 per cent. until required.

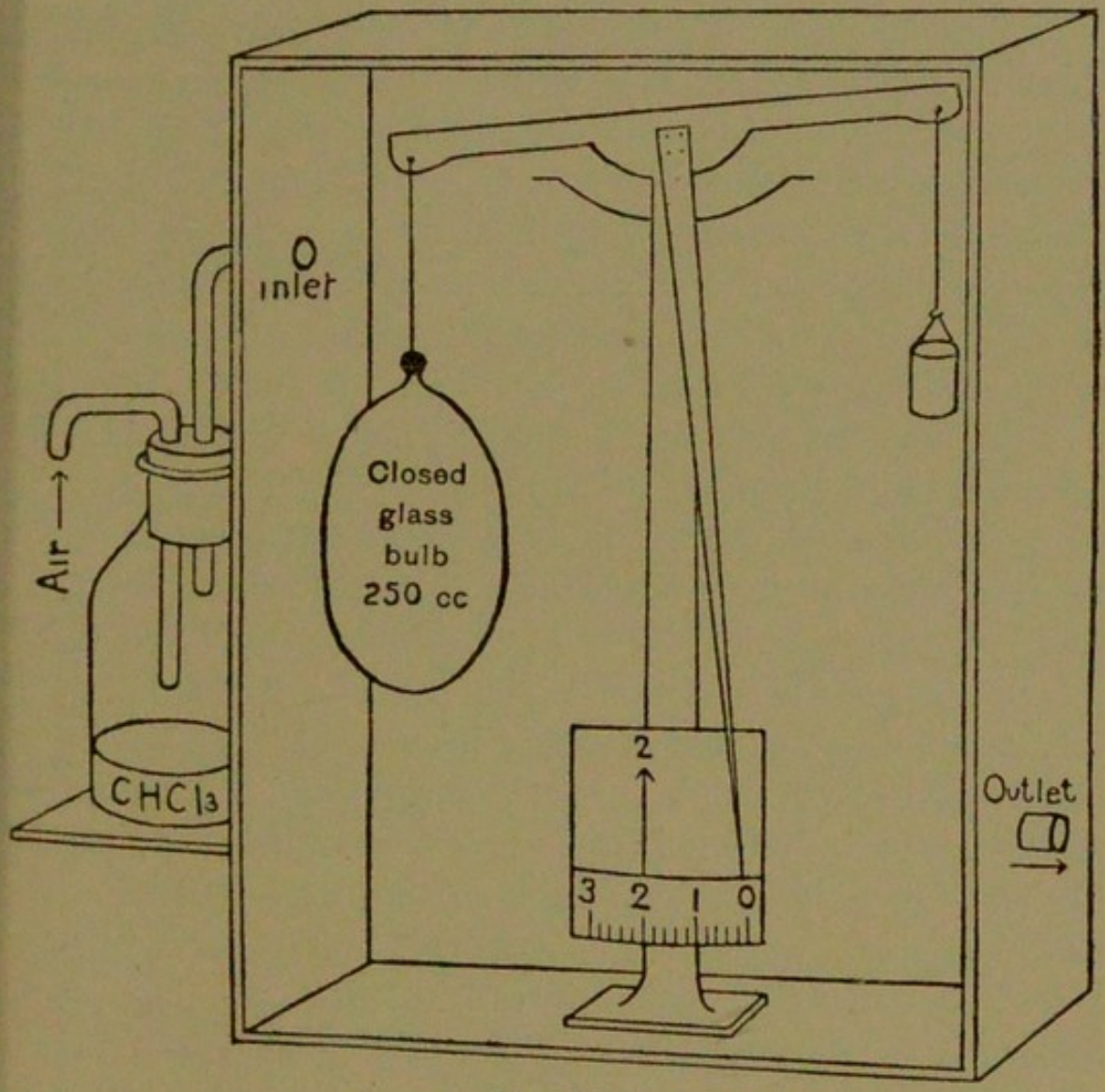


FIG. 51.—The Chloroform Balance.

Second step.—The anæsthetised animal is removed from the bell-jar or cupboard, for the operation of tracheotomy. The outlet tube of the mixing chamber is attached to the tracheal tube, and anæsthesia is maintained by a mixture

at about 1 per 100. The chloroform and air is taken in by the animal by its own respiratory movements, or supplied to the animal by the action of a pump. In either case the anæsthetic vapour is under slight positive pressure, *i. e.* it is delivered from the mixing chamber on the *plenum* system.

I shall at once anticipate the inevitable objection that this method is too troublesome for hospital use, by saying (1) that it is not too troublesome for daily use in the laboratory, for animals ; (2) that some thousand animals have been anæsthetised in my laboratory during the last six years, without the accidental loss of a single animal ; and (3) that even admitting that the procedure requires care, it is not too much to expect as much care to be bestowed upon the safe anæsthesia of a patient in a hospital, as is bestowed upon an animal in a laboratory. In point of fact the trouble of application would be smaller in the case of man, than it is in that of an animal.

The procedure in hospital is (or would be) simplified by the fact that the first step necessary in the case of animals, viz. the induction of anæsthesia in a confined space, is not required for the human subject. Obviously, also, tracheotomy is omitted ; all that is required for the human subject is an open face-piece or mask at the end of the delivery tube. For since the delivery of chloroform and air to the patient is on the plenum principle, and such pressure as exists in the mixing chamber and delivery tube is positive, length of tube is immaterial, and does not offer any obstacle to the inspiratory movements of the patient. All the apparatus required by the anæsthetist at the operating table consists of the tube itself and the face-piece or other terminal contrivance ; the pump, the chloroform bottle, the mixing chamber, and the chloroform

balance, are at a distance from the operating table—out of the way, but not out of sight. The size of the mixing chamber—30 litres—ensures the continuous and uniform supply to the patient, of chloroform (or ether) vapour at known and visible dilution. The indications of percentage are easily verified, and are visible to all persons concerned. The concentration, which by reason of cooling of the vaporising liquid automatically remains below 3 per cent., can be varied at will with sufficient rapidity, as shown by the indicator, and it cannot be suddenly augmented to a dangerous amount. The attention of the anæsthetist is free to be wholly bestowed upon the state of the patient, in accordance with which the strength of vapour is raised or lowered.

The apparatus in its laboratory form is not very portable. And although, no doubt, it may be practicable to render it more portable, I prefer at present to keep to the dimensions with which I am familiar, and to advise its use chiefly as a hospital fixture, set up in the operating theatre and in the room or rooms in which patients are prepared for operation. Obviously the apparatus is not meant for country practice ; it requires too much preparatory adjustment. If, as sometimes happens, I am asked to go and demonstrate this method of chloroform administration, I am obliged to ask for certain facilities, in default of which the administration cannot be carried out in a satisfactory manner. I must have a firm table or bracket for the chloroform balance, and a steady current of air propelled by a motor, and an assistant to mind the machine with ordinary intelligence. But to take the apparatus as it stands on the lecture table, and to set it up in makeshift fashion in a hospital, for use on a patient, would not be fair either to the patient or to the method. And I am not willing to make the attempt

under such conditions. All that I am willing to do here and now is to place a cat under a bell-jar, and show you after the lecture how thoroughly and precisely its chloroformisation can be performed and maintained.

I have finished. And I am sorry to have finished. As happens indeed every time we come to what we call "the end" of anything, we feel as if we had only just begun. How indeed, conscious of the endless questions that surround us, can we fail to feel that every end is also a beginning, in the procession of human thought and action—links in the endless chain of which we form part? How can we ever feel satisfied with anything we can know, or with anything we can do?

Yet in one respect, at the end of my task, I find that my anticipations have been more than fulfilled. I expected it to be a pleasant, if not an easy task. The interest that you have taken in it—after as well as during the actual "lectures"—the fact that some of you undertook to repeat, in the laboratory, experiments witnessed in the lecture theatre—has been to me a most stimulating experience, and has encouraged me to take full advantage of the invitation to make myself at home in this laboratory.

I thank you for receiving me so kindly, and I carry away with me the most agreeable memories of my visit to the University of California, and of the many friends and colleagues whose help has made my lecturer's task so easy for me. I should like especially to thank Professor Loeb, Professor O'Neill, Professor Setchell, Professor Maxwell, Dr. Robertson, and Dr. Burnett, and the laboratory assistants and students upon whose untiring goodwill the success of the lecture experiments has so largely depended—Mr. Moore, Mr. Wasteneys, and Mr. Antoni.

APPENDIX

THE UNIVERSITY OF LONDON

AND AN

IMPERIAL INSTITUTE OF SCIENCE

Being the substance of an address delivered to the University of California, Berkeley, Cal. U.S.A., on September 23, 1909

BY

AUGUSTUS D. WALLER, M.D., F.R.S.

(Late Dean of the Faculty of Science of the University of London)

Co-operation—The Conservative Principle and the Progressive Principle—Imitation and Initiation—The Method of Least Change and the Method of Experiment—Stagnation—The New Conditions—Education the most Radical of Interests—The Combination between Teaching and Research—University Research Fellowships—The First Duty of the new University of London—The Royal Commission, 1909*—The Faculties—An Object Lesson—An Imperial Institute of Science.*

THE custom that I find in force at this University is one that no man, however retiring of disposition he may be, can fail to obey. For it is a duty which I understand is never shirked, that any member of a Faculty, on returning from abroad, should report himself and his enlarged experience to a meeting of the whole University, and it is therefore no less a duty that cannot be shirked that a visitor from abroad should respond to the invitation to address the University on some topic that may be expected to be of common interest.

I have been informed that, coming as I do from the University of London—which to many people abroad, and indeed to some people in London itself, is a somewhat mysterious entity—it would be welcome that I should tell the University of California something about the University of London.

I shall not offer you an epitome of its calendar, nor of its past history, nor describe to you its colleges and schools, nor dilate upon its constitution and its government. Rather than attempt to describe the University of London as it was yesterday and is to-day, I prefer to direct my attention and yours upon its immediate future, and upon some of the first principles that determine

the healthy University in the healthy community—the *mens sana in corpore sano.*

I am not speaking now as a practical man, but as an idealist. Therefore I feel all the more free to confess as a first article of my University faith, that in last resort the motive of pure science must always be the practical motive, and that every student is required to render service to the community whose manifold services he enjoys. "Here's to the latest discovery, and may it never be of use to anybody," is not the thought to which I should ever say "hear, hear," even as an after-dinner sentiment.

"I want to know" is indeed the most natural of all expressions in the mouth of a student of science. To the practical man of affairs, of whom immediate and decisive action is required, what can be of more indispensable necessity than the clear and comprehensive knowledge that can rightly guide his immediate and decisive action? I believe that no man has ever been sufficiently sensible of this need until he has been placed in circumstances that have forced him to take action in the absence of such knowledge. And the medical profession, where the watchword is, or should be, "I want to help," is above all other professions that in which there is most call for mutual help between the man whose first duty is to know, and the man whose first duty is to help. The immediate aim of each is different, the ultimate aim of both should be the same—to contribute his best endeavour to the commonwealth of knowledge and of power. Yet the man who only "wants to know" is too prone to despise the practical requests of the man who "wants to help"; and the man who "wants to help" is too prone to ignore the service of the man who "wants to know." Each can help and teach the other, but the scientist must also want to help, as the physician must also want to know.

There is apt to be a kind of antagonism between the mind of the practical man and the mind of the scientific man. And if they never meet, that antagonism remains unopposed and futile or mischievous—the worst form of mental paralysis is *paralysis ignorans.* Let them meet, therefore—best of all let them meet in the common-room of their University—and from their opposed and complementary forces, new mental strength will arise in the service of the commonwealth. Their antagonism will become co-operative and effective.

Co-operative Antagonism.—We are apt to be fretted by opposition. Our opponent is so entirely in the wrong and so wilfully obstructive of our plans and efforts. But for his blind or malicious hindrance, it would have been so easy for us to "triumph over

difficulties." Not so. Opposition and difficulty are of the essence of all achievement. The obstacles that are enough to repulse the weak and worthless character, confirm, corroborate, and, it may be, exasperate the energy that is necessary to work and to success. Just clench your fist, and feel the muscles of your forearm while you do so; you will find that in the act not only the *flexor* muscles that bend your fingers are at work, but also the *extensor* muscles which are their antagonists.

To grasp the handle of a weapon the antagonism of your extensor muscles is as necessary as is the action of your flexor muscles. Firmness is a result of the co-operative antagonism of opposing forces. The strong measure requires an effective opposition as well as a powerful ministry, and so, if we must be fretted by opposition and criticism, let us be fretted and irritated and strengthened to justify the faith that moves us, rather than daunted and discouraged by the peculiar difficulties that seem to have gathered in *our* special path, and to be *our* special misfortune. And when we stumble, let us stiffen ourselves in the knowledge that a stumbling-block surmounted is a stepping-stone in an upward path.

The Conservative Principle and the Progressive Principle.—There are two great principles involved in the welfare of every living thing—of every organised mass—whether man or nation, trade or profession or art or science, church or college or university—namely, the conservative principle and the progressive principle—the principle of imitation, and of obedience, and of heredity—the opposite principle of initiation.

Imitation and Initiation.—Any organised living mass—be it a single animal or an organised body of men—by virtue of the conservative principle of heredity, of repetition of like by like, of imitation of action that has achieved success, of obedience to custom that has survived—works at smaller cost than if each individual organism had perforce to work out afresh its own salvation, evolve by itself its own fittingness in the service and mastery of its surroundings.

But the child that can only imitate and repeat the actions of its parents and teachers, contributes nothing to the excellence of the family and of the nation and of the race. The upward progress of each and every community requires the costly flame of initiative and discovery and invention, the burnt offerings of talent and of genius at the altar of the common wealth and health.

The apprentice must first learn at the feet of his masters, believe what he is told, imitate what he sees done, copy good models, be the echo and the assistant of the experienced craftsman along well-beaten paths. But life is short and the arts are complicated, and

even the apprentice who is never to become more than an efficient journeyman, still more so the apprentice of rarer clay who shall contribute to the commonwealth of knowledge and of power, is required to be something more than the faithful imitator of his teacher. He will be required to initiate; he should learn early from his teacher, by example rather than by precept, that the end and aim of his apprenticeship is not merely the actual knowledge and skill that experience can confer, but the ability of his own brain to deal with new or unexpected conditions.

In all provinces of human activity, success is a resultant of the happy blend between these two complementary principles—imitation, the conservative principle—initiation, the progressive principle. But while, in all provinces, the conservative element—being, so to say, the means and the consequence of wholesale economy in nature—must bulk the larger, the progressive element, as the activating ferment that animates the mass, weighs but little in the scales of practical life. Yet fortunately, perhaps, while the pure ferment is of such rarity and tenuity that it fails sometimes to turn the scale even in the laboratory, it is the all-pervading and quickening leaven; and the rough goods of the market-place contain it and carry it abroad in the unceasing stream of useful applications to human wants.

The Method of Experiment and the Method of Least Change.—In every province of human activity—and in particular in that whereby knowledge, and the power to use knowledge, are continuously transmitted from generation to generation, namely, in the province of education—the faculty of imitation is easier to exert and easier to develop than is the more costly and more capricious faculty of initiation. Yet this rare and costly and, we must add, dangerous ingredient is of primary necessity in education. "Dangerous" we have said. Yes. Since we cannot surely tell, among the countless novelties issued from the genius or the vagary of the exceptional brain, which may be the hits and which the misses, among all the innumerable projectiles by which our attention is solicited.

But while this extreme can be dangerous, there would seem to be very little danger in England of our running the risks inseparable from experiment and innovation. For the genius of our nation is a practical genius, that looks upon the conservative way as the better way, and makes its changes as slowly as may be by gentle gradient from precedent to precedent. That is the safe and easy way, the way of nature, and to this preference of fact copied over fancy tried, may fairly be ascribed our own constitutional prosperity. We fight shy of the logical conclusions of the

doctrinaire, and of the leap in the dark that seems to him so sure and so safe. We prefer to imitate the method of nature, the conservative method of least change.

Stagnation.—Yet there is danger in every extreme, even that of caution and "safety," and in our case the greater danger would seem to be on the conservative side of the beam, towards stagnation, rather than on the progressive side of innovation and experiment. We have been a most favoured nation in the great development of transport that has characterised the last century of the world's history. We still enjoy the fruits and the satisfactions of our good fortune and of our energy. But one may have too much of a good thing, if satisfaction should be permitted to blunt intellectual initiative, and to relax the practical endeavour to continue to excel.

We assuredly err on the conservative side in our educational methods. We are educated and governed by the time-honoured methods, of which the key-note and dominant chord are imitation and repetition and dialectics and old customs, to the almost universal exclusion of that most costly, dangerous, yet most valuable ingredient of human life, originality of thought and of enterprise.

The New Conditions.—These are the most characteristic qualities required by the new conditions of life, where men move in large masses, and control large measures of the energy surrounding them. We need in the international struggle for welfare and for existence, knowledge and power commensurate with the forces placed in our hands by the modern applications of physical science.

And the roots of applied science are pure science. And the propulsive force in the roots and trunk and branches of each living tree, as in every organism—be it science or art or craft, man or college of men or nation—is in last resort the quality and the character of the units constitutive of that organism, their specific power of initiative, added to the excellence of the heritage to which the initiative of their ancestors gave birth.

Education the most Radical Interest.—Education is the most radical of all interests. Granted that it must be true to nature as to its conservative principle. But let us also clearly recognise that education, now more than ever, requires to be urged still further in obedience to the progressive principle—namely, in the direction of teaching the pupil to use his own mind in his profession, rather than to copy the mind of his professors. Yet since to copy and to imitate is in a measure the lot of all men, and the brain of the most

original thinker is but a field in which other men's thoughts have germinated and multiplied; and since perforce to copy and imitate is the first and most natural act of life, let us insist that our professors and teachers shall themselves use their own minds, and not suffer themselves to drop into the easy jog-trot of routine or pedantry. No doubt we want our professors to be *learned* men, but we also want them to be *learning* men, since they are the living models set before the minds of the rising generation.

The Combination between Teaching and Research.—It is upon the combination between teaching and research, and not upon their separation, that the intellectual welfare of a community and of an individual depends. For while it is a fact that one man may be the discoverer for himself alone, rather than the discoverer to others, and that a different man may possess special excellence as the interpreter and mouthpiece of other men's discoveries, it is no less true that the best guide to any district of knowledge is the man who has been there himself as an explorer or as a pioneer. It is in the blend between research and teaching that both research and teaching find their most effective expression. And in the resultant effect, it is difficult to say which of the two elements is the more essential. The combination between them may be compared to that of common salt, in which both elements are necessary to the qualities of the compound. All good teaching involves research, all good research involves teaching. Faraday was at once a great inquirer and a great teacher, and in lesser degree every inquirer is a teacher, every teacher is an inquirer. The professor, reader, lecturer, or tutor who fulfils his task as a mechanical repeater of dicta and dogmata, is of hardly greater value than a text-book read aloud. The teacher who is also an active searcher and learner reacts upon his pupils with the convincing power of reality and of example; the combining power of his thought is that of active thought—thought in its nascent state.

University Research Fellowships.—It is to the credit of the new University of London that in the official recognition of its teachers the first qualification required on behalf of any man or woman who asks to be recognised as a University teacher, is evidence of ability to increase knowledge by his own investigations—and further, that in the case of young teachers, where proof of such ability has not yet been given, but may reasonably be expected, a system has been adopted of "recognition on probation" for a limited time, provided that the conditions of work are

such as to permit the "probationer" to fulfil his promise, and give proof of his ability to acquire knowledge at first hand by his own investigation. This excellent system might well be further developed; the active young teacher in a polytechnic, on a minimum salary of £150 and a maximum teaching time of 500 hours, would feel that the University was indeed helping, and not hindering his efforts, if his "probationary recognition" not merely required conditions protecting him in his own interest from overteaching at an underwage, but actually carried with it conditions forwarding his self-development, and justifying his sense of fellowship in and loyalty to the University in which he is recognised. A "minor research fellowship" of £50 from the University chest, added to a teacher's salary of £150, would be in every way an appropriate and a remunerative expenditure of University funds; its direct return would be secured in the form of a higher average teaching power, apart from the accidental and incalculable return in the form of exceptional genius helped to earlier distinction, under conditions more favourable than at present to the mental development of the teacher during the best years of his life. Not to speak of the Colleges and Schools of the University, there are at present in the Polytechnics alone upwards of 60 recognised University teachers. Can it be doubted that the allocation of £1000 in the form of twenty "minor research fellowships" would be hardly less valuable in the interests of the University and of the community than that of the same sum to a single University Professorship? Excellent as has been the allocation of the County Council Grant of £10,000 per annum to University Professorships, it is extremely desirable that it should be expanded and extended over a wider area. No one acquainted with the relations between the University of London and its several Colleges, Schools, and Institutions, can doubt that the return to the University in the form of real influence and power, through the good-will and loyalty of its recognised teaching staff, would become incalculably extended by the carefully administered distribution of research fellowships among a teaching *personnel* that includes the picked men of what is actually a *corps d'élite* of capable and ambitious young men throughout the Metropolis. These picked men have proved their value and capacity under often adverse conditions, and against obstacles that have served to test their mettle; they are marked as eligible for further promotion by the fact that they have received recognition as teachers of the University. And looking forward to the future in the light of the past, is it not a wise policy that the University should broaden its base in the community and cast its net wide?

Is not the Faraday of the future as likely to be found among the ranks of the ambitious young teachers of Polytechnic schools, as among those of the equally ambitious, if more favoured and less strenuously tried teachers in the Schools and Colleges of the University? But I do not desire to imply that any distinction of class or kind is to be admitted between recognised teachers of school, college and institution, when the status of recognised teacher is in itself a distinction, and a token that the person so distinguished has excelled his fellows in ability and in working power. I would have accessible to all such teachers alike, not only minor research fellowships of the University on a lower scale of emolument, but full fellowships on a higher scale. I would have ordinary as well as minor fellowships, fellowships of £200 as well as fellowships of £50, from which, in correspondence with the higher scale of remuneration, a correspondingly higher standard of value should be the return, both as regards the work done by the recipients, and as regards the consolidation of University influence upon the whole body of recognised teachers in the Schools and Colleges. Beyond this stage of full fellowship, at the Professorship grade, the University teacher appointed and paid by the University can be left to work out his own intellectual salvation, and as a student among students, to contribute to the common welfare.

The First Duty of the new University of London.—The first duty of the University is not to favour this or that College or School by the allocation of the scanty resources over which it has control, to ordinary College professorships or lectureships, but to strengthen itself, and at the same time the whole field of its influence, by devoting its resources to the direct encouragement of research in association with teaching, and to the centralisation by that agency of the intellectual forces now scattered in these Colleges, Schools, and Institutions.

I am not pleading for the separate endowment of research, but for the further official recognition of research as an integral constituent of normal teaching at all grades of the University programme. Indeed, so far from urging that the "University research fellow" should devote the whole of his time to research, I should support the precisely opposite principle, and insist that some portion of his time should be devoted to teaching. It is upon regular teaching in some form that the average researcher must ultimately rely for his regular livelihood. This is especially so in the Faculty of Science, and in that of Medicine, since the Hospital physician and surgeon is, above all, a teacher of the principles and practice of his profession. It is less so in other faculties which serve in greater

measure as the channels and ante-chambers of the practical and commercial and legal and political professions.

But in any profession there is no mental gymnastic more valuable to the mind of the researcher than the instruction of other minds in the field of knowledge to which his own special interests belong.

The Royal Commission.—The organisation of the University of London is now under the scrutiny of a Royal Commission. The field covered by its reference is vast and complicated, and the task of reviewing and co-ordinating the local interests of the various colleges, schools, and other institutions, more or less closely connected with the University, is likely to be heavy and lengthy. I do not propose to enter upon any discussion of these various interests, nor to suggest any scheme for a reconstitution of the University of London. But in connection with "the provision for teaching and research that should exist in the Metropolis, and their connection with similar provisions existing in other parts of the United Kingdom and of His Majesty's Dominions beyond the seas," I shall sketch a scheme that commends itself to my mind as a concrete and feasible outcome of the foregoing considerations.

The teaching *personnel* of Colleges, Schools, and Institutions of the University of London form as many separate groups of men (and women) very slightly attached to "the University." These groups may be pictured as a collection of variously coloured strands more or less loosely attached to an imaginary central point called "the University"; of these several groups, two principal groups—University College and King's College—form a distinct and united body at this point—they have incorporated themselves there, and without any surrender of College identity, are by reason of that "incorporation" entitled to be regarded as the commencing embodiment of a true University. A third group, the Imperial College of Science and Technology, is nominally a School of the University, but, in reality, is entirely independent of its control, and, as far as we know, desires to remain so. Other groups—the Medical Schools, the London School of Economics, the East London College, the Birkbeck College, the three Women's Colleges, the six Polytechnics, are loosely tacked on to the imaginary point called the University of London. The collective value of the stuff in these disconnected strands is very great, but it is in great measure wasted for lack of a transverse bond of union threading together the strands themselves. That bond of union, by which the loose fabric should be knitted together, should be found in the Boards of Studies and Faculties of the University,

which are the groups of teachers with like interests, attached to the several colleges, schools, and institutions.

The Faculties.—The organisation of these groups on Faculty lines, which are to be regarded as lines transverse to the lines of colleges and schools, would form as it were woof to web in the fabric of a real university.

The stuff of which any University is formed consists of men and women; they are at present organised on College lines; what is required to knit them together into a University fabric, is a further organisation on Faculty lines. This further organisation is by no means difficult of accomplishment; its lines are already laid down in Boards of Studies, and the financial support, without which no policy or enterprise can be sustained, is not of any forbidding magnitude. University research fellowships, tenable by recognised teachers of the University, would afford a means of forming, from the Boards and Faculties, lists or panels in various subjects, the members of which as "research fellows of the University," should be liable, when called upon, to deliver at the head-quarters of the University, courses of lectures on subjects of which their own investigations had rendered them authoritative exponents. It is during the first ten or fifteen years of his teaching career that the teacher's mental activity is keenest and that his quality is made apparent. I would, if funds permitted, definitely recognise and encourage the development of power of such a teacher, by the allocation to him of a research fellowship that should be expected to occupy half his working time, and to supply him with half his living wage, and that should cause him to bring to the central lecture theatre of the University real additions to knowledge, and to the lecture theatre of his school augmented mastery of the subject he has to teach. I can imagine no condition of life more enviable than that of a keen-brained man or woman, during the best ten years of intellectual life, from, say, the age of twenty-five to that of thirty-five, in receipt of a salary of £200 for teaching during half the week, and of a fellowship of £200 for "researching" during the other half. I am convinced that under such conditions of life the return in teaching power would repay the outlay in money, and that from among the workers thus supported, the exceptional man or woman would be far more likely to emerge than is the case under our present conditions.

Quite independently of the interests of the exceptional mind—which being exceptional cannot be expected to be of frequent occurrence—it is by the general levelling-up influence to be secured

by the encouragement of individuality of thought throughout the teaching *personnel*, that the return of value for value expended would be most certainly assured.

An Object Lesson.—The University of London is not altogether without experience in the direction of intercollegiate centralisation on Faculty lines. The Physiological Laboratory, to which some years ago it devoted a portion of the somewhat limited space placed at its command in the Imperial Institute building, can be appealed to as an object lesson, on a small scale, of the principles that should be applied to the more comprehensive organisation. Its teaching *personnel* consists of a panel of University lecturers, liable to be called upon, when convenient to themselves and to the University, to deliver a course of eight lectures upon a special department of science with which they are acquainted at first hand, and in which they are of recognised authority. The panel, at present composed of thirty-seven persons, consists of (i) the recognised teachers of the University, and (ii) other distinguished experts in science, from the United Kingdom and from the Dominions. Of these thirty-seven members, eighteen are recognised teachers of the University of London; six are distinguished specialists living in London; eight are teachers in the Universities of Oxford, Cambridge, Liverpool, and Bristol; and five are professors and experts belonging to Toronto, Winnipeg, Johannesburg, and Alexandria.

The Committee of Management is a mixed Committee, composed of (i) members of the Senate, (ii) other persons interested in this particular aspect of University life. The category of "other persons" includes members chosen by reason of their knowledge of and interest in its subject matter, as well as members interested to the extent of fulfilling the functions of the pious founder; and in this category of "other persons" are to be found the most valuable servants of the University of London. I think it may be permissible to name them in connection with this particular object lesson. Sir Lauder Brunton, having no other official connection with the University, is the Chairman of the Committee; Sir Walter Palmer, as a graduate in Science, interested in the welfare of Science and in the general welfare of the University, defrayed the equipment expenses of the Laboratory. Thus as regards administration, this department of the University, while subject to the ultimate authority of the Senate, is not under the exclusive control of any one party or college or school, but is guided in the most absolutely smooth and harmonious manner by a mixed Committee of members of the Senate and other distinguished persons, with whom the sole object is the efficiency of the department in the interests

of the University, and from what I have said, it is clear that the interests of the University are not viewed solely in an exclusively local sense, but with distinct bearing upon "the facilities for education and research which the Metropolis should afford for specialist and advanced students in connection with the provision existing in other parts of the United Kingdom and in His Majesty's Dominions beyond the Seas." I have quoted the words of the reference to the Royal Commission appointed this year on the organisation of the University of London. The rough sketch that I have just given of the constitution and working of a University organisation, is the description of what has been actually going on for the last eight years in the Imperial Institute, and as a department of the University of London.

In other subjects—notably in Botany, Geology and Zoology, an organisation of advanced lectures on similar lines has taken place, and only requires, for its proper development, facilities similar to those that have been enjoyed by Physiology.

An Imperial Institute of Science.—It is essential to the success of such an organisation that it should be from the outset concentrated and centralised by the University itself, in lecture rooms and laboratories and libraries under its direct control. If the organisation of panels of research fellows of the University is to be common to all the teachers of all its Colleges, Schools, and Institutions, its local habitation must be at the University itself, not at any one or more of its colleges. In this connection, as well as in connection with the provision required for teaching and research "in the Metropolis, in the United Kingdom and in the Dominions beyond the Seas," the Imperial Institute at South Kensington is clearly indicated as the proper habitation of a college of men drawn from among the active teachers in the Metropolis, in the United Kingdom and in the Dominions.

All the materials are ready to our hand for the foundation of an Imperial College of Learning and Science, that should one day become in relation to British Learning and Science what the Collège de France has been and is in the intellectual life of France, and fulfil the purpose for which the purchase of the South Kensington Estate was recommended fifty-eight years ago by the late Prince Consort.

The building stands ready amid a group of active Colleges, occupied partly by the offices of the University, partly by the offices of the Imperial Institute itself. But in both parts, the natural and fitting service that it ought to fulfil is foreshadowed by active laboratories which have arisen in it as the natural and fitting organs of an Imperial Institute of Science. What nobler service

could be assigned to the Imperial Institute than that of an Imperial Institute of Science and Learning, a central meeting-place of an intellectual *corps d'élite*, composed of the most active learners and teachers of the Metropolis and of the United Kingdom and of His Majesty's Dominions beyond the Seas?

The building was intended as an Imperial Institute of Commerce; that intention has not been fulfilled, and cannot be fulfilled at South Kensington. Yet, if we believe that Commerce rests upon applied Science, as applied Science rests upon pure Science, is it not an even wider fulfilment of the original purpose, and a fuller satisfaction of the generous support of that purpose from all quarters of the British Empire, to form an Imperial Institute of Science as a provision in the Metropolis for University teaching and research, and as "a facility afforded by the Metropolis for specialist and advanced students in connection with the provision existing in other parts of the United Kingdom, and of His Majesty's Dominions beyond the Seas"—an Imperial clearing-house of knowledge?

To recapitulate the whole argument—

The quickening factor of initiative—*i. e.* of research—must permeate the substance of the receptive and imitative element in teaching. Research and teaching form an indissoluble compound, each a necessary complement of each. Research apart from teaching, teaching apart from research, are equally unnatural and comparatively ineffective factors. It is essential to the welfare and efficiency of a University, and especially so in the case of the University of London, that in the organisation of its teaching staff at all grades, effect should be given to this dual principle—no research without some teaching; no teaching without some research.

The practical measures by which it is possible to give effect to this dual principle in London are such as would at the same time constitute an intercollegiate bond of union formed by the University between its Colleges, Schools, and Institutions through its Faculties and Boards of Studies.

The formation of this bond or union should consist in the foundation of an Imperial Institute of Science and Learning, of which the present Imperial Institute building should be the home and head-quarters, and its *personnel* select panels of University Research Fellows. Such panels should consist of professors, recognised and probationary teachers, and other distinguished persons in London, in the United Kingdom and in His Majesty's Dominions beyond the Seas, selected and nominated by Boards of the Faculties, appointed by the University.

NOTES

(Note 1, p. 8.) *The muscle method.*—I have given considerable attention during the last year to the investigation of the comparative action of drugs by means of this method, which I believe to be capable of considerable extension and of relatively simple application. The results so far obtained have been given in the following publications—

"The Physiological effects of (1) Primary and Secondary Propyl Alcohol, (2) Normal Primary and Tertiary Butyl Alcohol," *Proceedings of the Physiological Society*, July 1908 (in *Journal of Physiology*, vol. xxxvii.).

"Action of Salts on the Contractility of Isolated Muscle," *Ibid.*

"The Comparative Effect upon Striped Muscle of Alcohol, Ether and Chloroform," *Ibid.*

"The Comparative Power of Alcohol, Ether and Chloroform as measured by their Action upon Isolated Muscle," *Proceedings of the Royal Society, B.*, vol. 81, p. 545, 1909.

"Action of some Alkaloids upon Striated Muscle. I. Muscarine and Atropine," *Proceedings of the Physiological Society*, November 1908 (in *Journal of Physiology*, vol. xxxvii.).

"The Action of Digitaline and Allied Substances upon Striated Muscle," *Ibid.*, December 1908 (*J. of Physiol.*, vol. xxxviii.).

"Action of Cinchona Alkaloids on Muscle," *Ibid.*, October 1909 (*J. of Physiol.*, vol. xxxix.).

"Action of Stovaine and Cocaine on Muscle," *Proceedings of the Royal Society*, December 1909.

"Action of the Nux Vomica Alkaloids (Strychnine and Bucine)," *Proceedings of the Physiological Society*, December 1909.

"The rate of Action of Drugs on Muscle as a Function of Temperature," *Ibid.*

"The Action of Aconitine (and Allied Alkaloids) on Nerve and Muscle," *Journal of Experimental Physiology.*

"Certain Physical and Physiological Properties of Tetrachlorethane and Trichlorethylene," *Proceedings of the Royal Society.*

Method.—The two sartorius muscles of a frog are dissected out and the portions of bone to which they are attached are ligatured with fine copper wires serving as conductors. The muscles are set up in the two vessels V, V and connected with two myographic levers that record their movements on two smoked plates L, R. The connections with the secondary coil of an inductorium (Berne model) are as given in the diagram, so that both muscles are traversed in series by the same current in the same direction. The muscles are directly excited once every 10 seconds by maximal break induction shocks. Each observation consists of three parts : a first part consisting of the normal responses of the muscle im-

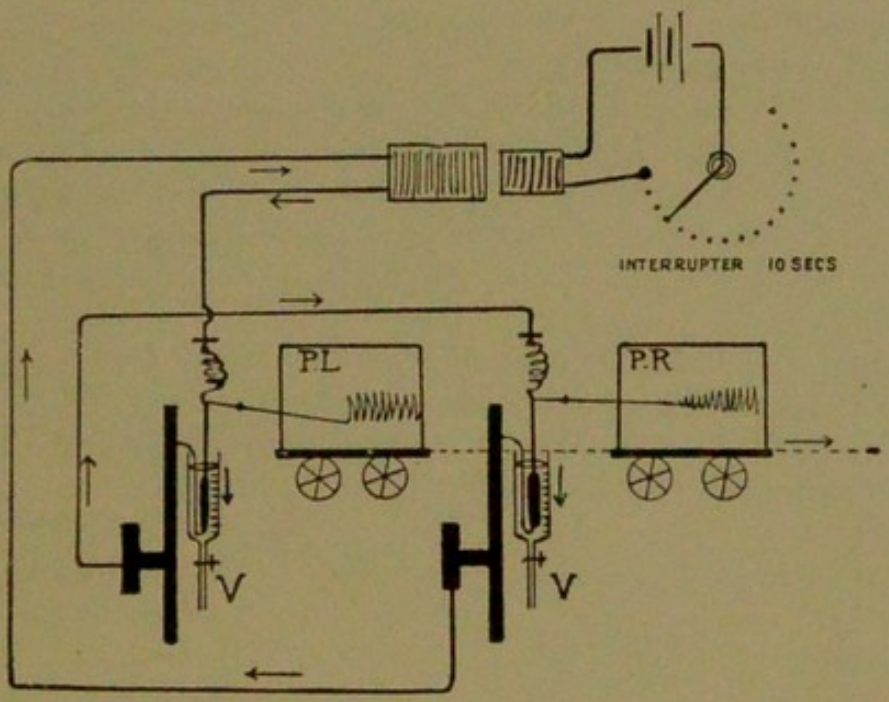


FIG. 52.—Double Myograph to test Action of Substances in Solution.

mersed in normal saline (0·6 per 100 NaCl in tap water) ; a second part consisting of the responses while the muscle is immersed in an experimental solution ; a third part consisting of the responses while the muscle is replaced in normal saline. The solutions are changed by being run off through a tap and run in from a pipette, care being taken that the volume of fluid is always the same. The induction currents are kept going automatically throughout an experiment, excepting during the short periods required for changing the solution.

The following table contains a summary of the relative toxicities of the monatomic alcohols of the paraffin series according

to different observers. The last column is derived from observations on isolated muscle.

	Joffroy	Picaut	Dujardin	Barr	A.D.W.
$CH_3 \cdot OH$, Methyl Alcohol	0·46	0·66	1·17	0·8	0·5
$C_2H_5 \cdot OH$, Ethyl „	1·00	1·00	1·00	1·0	1·0
$C_3H_7 \cdot OH$, Propyl „	3·50	1·00	2·00	2·0	4·0
$C_4H_9 \cdot OH$, Butyl „	8·00	3·00	4·20	3·0	8·0
$C_5H_{11} \cdot OH$, Amyl „	18·50	16·00	5·00	4·0	16·0

From a considerable but by no means sufficient number of observations on muscle, I drew up the scale of toxicity given in the last column of the above table.

Professor Loeb tells me that according to more recent observations the scale, taking ethyl alcohol as 1, comes out $\frac{1}{3}$, 1, 3, 9, 27. The difference between the two results, considering the differences of method, etc., is not excessive, and may perhaps have been occasioned by actual differences of alcohols employed.

A short but carefully taken series of comparisons between primary and secondary propyl and butyl alcohols made last year at the University of London, showed definitely that the order of activity of the four butyl alcohols is :—

1. Normal primary butyl alcohol
2. Iso-primary „ „
3. Secondary „ „
4. Tertiary „ „

I have taken a considerable number of records during the last year, with Dr. V. H. Veley, of the action of various alkaloids and other substances upon isolated muscle.

From a first review of our results we have drawn up the following table of the relative molecular toxicity in this respect of the substances we have dealt with, to serve as a first standard of reference for further investigations.

The principle upon which this table has been drawn up is given in the text in connection with the experimental comparison of alcohol, ether and chloroform ; it is here extended to other groups of substances in solution more or less dilute.

On the scale we have adopted, we expect for a substance of low toxicity, *i.e.* below 100, to obtain abolition of muscular contrac-

	Molecular weight	Molecular toxicity
Aconitine	645	1000000
Quinine	324	100000
Quinidine	324	50000
Cinchonine	294	25000
Cinchonidine	294	25000
Cinchonamine	296	400000
Muscarine	137	about 5000 ?
Atropine	280	about 2000 ?
Papaverine	351	66000
Alcohol	46	60
Ether	74	720
Chloroform	119·4	6000
Strychnine	334	12000
Brucine	406	4000
Cocaine	303	40000
Stovaine	235	40000
Methyl Stovaine	249	40000
Piperidine	85	16500
Nicotine	162	33000
Pyridine	79	3000
Picoline	93	3000
Theobromine	180	18000
Caffeine	212	12000
Caffeotannic acid	326	1500
Curarine iodide	424	about 5000 ?
Chloralhydrate	165	1200
Butylchloralhydrate	193	2400
Trimethylamine	59	12000
Ammonium hydrate	32	3000
Antipyrine	188	500
Hyoscyamine	298	600
Gelseminine	366	60000
Eserine	275	50000
Sodium hydrate	46	3000
Potassium hydrate	56	6000
Hydroxylamine	33	4000
Hydrochloric acid	36·3	17000
Formic acid	46	7000
Acetic acid	60	7000
Propionic acid	74	4000
Oxalic acid	90	7800
Tartaric acid	150	8200

tility at ordinary room-temperatures at the end of between five and ten minutes' immersion in a solution of molecular or "normal" concentration, *e.g.* in a 46 per 1,000 solution of ethyl alcohol.

For an approximately equal result with a substance of toxicity = 1,000, 10,000, 100,000, we should take the solutions of decimolecular, centimolecular, and millimolecular strength (see p. 129).

To convert a value given on the normal or molecular scale to the corresponding value by weight (in grammes per 100), we have to divide the molecular weight by the dilution × 100, *e.g.*, a $\frac{n}{1000}$ solution of nicotine (m.w. = 162) is a 162 per 1000 × 100 or 0·00162 per 100 solution by weight.

To convert a value given in grammes per 100 to the corresponding value on the normal scale, we have to divide the percentage number × 10 by the molecular weight, *e.g.* a 0·02 per 100 solution of nicotine is a

$$n \,.\, \frac{0{\cdot}02 \times 10}{162}, \text{ or } n \,.\, 0{\cdot}00123.$$

In the case of a salt, *e.g.* nicotine tartrate, we must be careful to distinguish between normality considered in terms of the compound or of the base only.

Thus the molecular weight of nicotine tartrate being 162 + 336, a $\frac{n}{1000}$ of nicotine is given by 0·00498 gramme per 100 of nicotine tartrate.

Similarly the molecular weight of curarine iodide being 297 + 127, we require to take 0·00424 gramme per 100 of the compound to obtain a $\frac{n}{1000}$ solution of curarine reckoned as base. Vice versa a 0·01 per 100 solution of curarine iodide is a $n \,.\, \frac{0{\cdot}01 \times 10}{424}$, or n . 0·000236 solution of curarine reckoned as base.

I do not assume from this scale of toxicity in connection with one particular tissue that a similar scale holds good for an entire organism. That can only be learned from direct experiments on the entire organism, as regards which one of the readiest and most convenient signs is the effect upon arterial blood-pressure. I have made, with the assistance of Mr. W. L. Symes, comparisons of

this nature[1] in the case of alcohol, chloroform and ether, with the following result—

	Physiological equivalence gauged by the sartorius muscle	Physiological equivalence gauged by the effects on blood-pressure by intravenous injection
Chloroform .	1 gramme	1 gramme
Ether . .	8 grammes	8 grammes
Alcohol .	40 grammes	32 grammes

T. C. Burnett ("The Influence of Temperature upon the Contraction of Striped Muscle and its Relation to Chemical Reaction Velocity," *Journal of Biological Chemistry*, vol. ii., No. 3) obtained, as the result of observations of the latent period, between about 5° and 35°, that the duration was reduced to $\frac{1}{2}$ or $\frac{1}{3}$ for every rise of 10°.

V. H. Veley and A. D. Waller.—The Rate of Action of Drugs on Muscle as a Function of Temperature.

We have recently tested the problem by observations on the rate of action on muscle of alcohol, chloroform, quinine and aconitine at temperatures between 7° and 25°. We used Esson's formula, modified for our purpose, for the calculation of results—

$$\log L_0 - \log L_1 = m(\log T_1 - \log T_0)$$

(where L_0 and L_1 are the lengths of time between application of the drug and cessation of contraction, and T_0 and T_1 the absolute temperatures at which the action took place. m is the experimental constant).

The values of m came out as follows—

Alcohol = 20·5, chloroform = 14·3, quinine = 26·7

(the value of m in the case of hydrogen peroxide and hydrogen iodide = 20·38, and in that of chloric acid and ferrous sulphate = 26·5).

The corresponding temperature-coefficients per 10° are—

Alcohol = 2·02, chloroform = 1·63, quinine = 2·52.

(In a previous rough determination we found ether = 2.)

The data from which the value of m was calculated in the case of chloroform are as follows—

[1] Report of a Committee of the British Association, Appendix VI, Section I, Winnipeg, 1909.

Temperature	Length of time of abolition	$\log \frac{T_1}{T_0}$	$\log \frac{L_0}{L_1}$	m
7°	24·5 min	·0000	·0000	—
10°	21 ,,	·0047	·0670	14·3
19°	13 ,,	·0182	·2753	15·1
24°	11 ,,	·0257	·3478	13·5

The value of m arrived at by Esson's formula corresponds with $\frac{1}{555}$ of the value of the constant μ calculated by the more generally employed formula of Arrhenius.

The range of temperature within which experiments can be made is sufficiently limited to allow the data to be dealt with

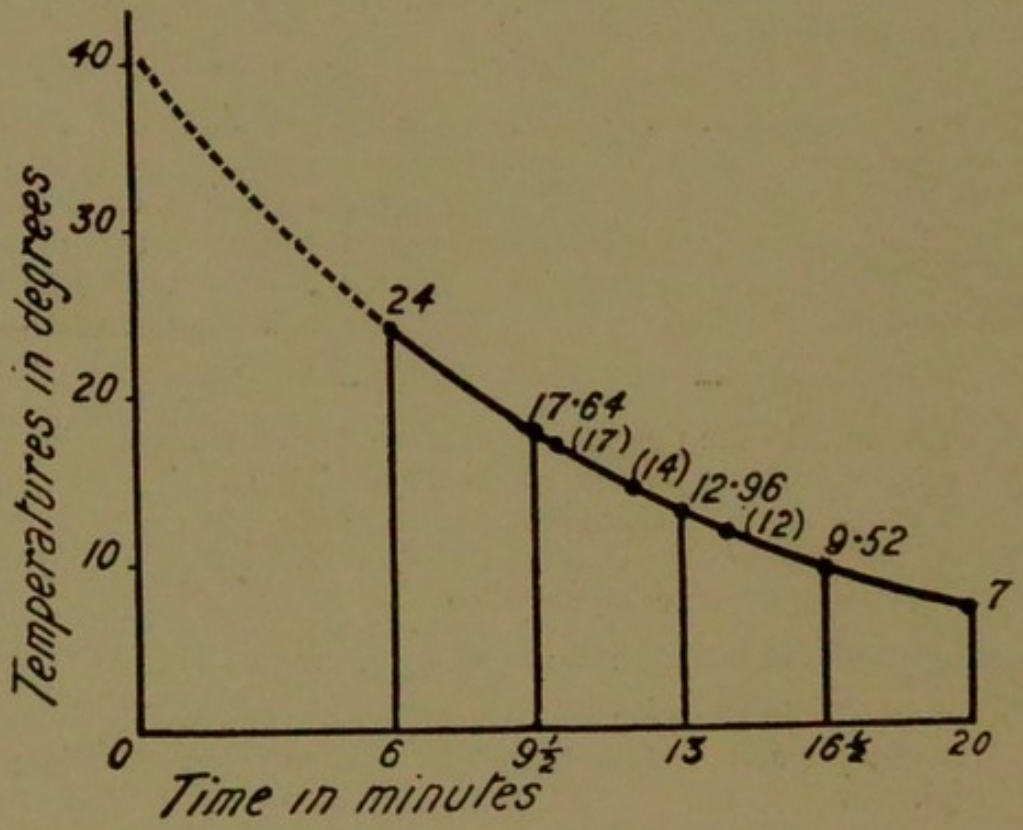


FIG. 53.—Alcohol.

graphically on squared paper without the use of mathematics other than simple arithmetic. We shall find it convenient to plot times in minutes along the abscissa, temperature in degrees along the ordinates.

Taking, *e.g.*, the following results of a series of experiments at

different temperatures with a normal solution of ethyl alcohol, viz.—

at 24°, abolition in 6 minutes
„ 17°, „ „ 10 „
„ 14°, „ „ 12 „
„ 12°, „ „ 14 „
„ 7°, „ „ 20 „

we begin by plotting the ordinates 24 and 7 at the times 6 and 20.

Between the two points we then plot a theoretically correct geometrical curve, taking for our ordinate at the middle point between 6 and 20, *i. e.* at the 13th minute, the value of the geometric mean between 24 and 7.

$$\frac{24}{\text{mean}} = \frac{\text{mean}}{7}$$

$$\begin{aligned} \log 24 &= 1{\cdot}3802 \\ \log\ 7 &= \underline{\cdot 8451} \\ 2 \log \text{mean} &= 2{\cdot}2253 \\ \log 12{\cdot}96 &= 1{\cdot}1126 \end{aligned}$$

In a similar manner we find and plot the values of the ordinates at the middle points between 6 and 13 and between 13 and 20, *i. e.* at $9\frac{1}{2}$ and at $16\frac{1}{2}$—

$$\frac{24}{\text{mean}} = \frac{\text{mean}}{12{\cdot}96}$$

$$\begin{aligned} \log 24 &= 1{\cdot}3802 \\ \log 12{\cdot}96 &= \underline{1{\cdot}1126} \\ 2 \log \text{mean} &= 2{\cdot}4928 \\ \log 17{\cdot}64 &= 1{\cdot}2464 \end{aligned}$$

$$\frac{12{\cdot}96}{\text{mean}} = \frac{\text{mean}}{7}$$

$$\begin{aligned} \log 12{\cdot}96 &= 1{\cdot}1126 \\ \log\ 7 &= \underline{\cdot 8451} \\ 2 \log \text{mean} &= 1{\cdot}9577 \\ \log\ 9{\cdot}52 &= \cdot 9788 \end{aligned}$$

Joining the tops of these ordinates we have a true geometric curve, 24, 17·64, 12·96, 9·52, 7·0, with which we can compare our actual data, viz. 17° at 10 min., 14° at 12 min., 12° at 14 min., which, as we see, fall upon the curve drawn between 24° at 6 min. and 7° at 20 min.

Constructed on this plan, the curve exhibits very plainly how the toxic effect takes longer and proceeds more slowly at low than at high temperatures. In the present example abolition of contraction takes 20 min. at 7° and 10 min. at 17°, *i. e.* by a rise of 10° the time of abolition is halved and the velocity of abolition is doubled.

(Note 2, p. 12.)

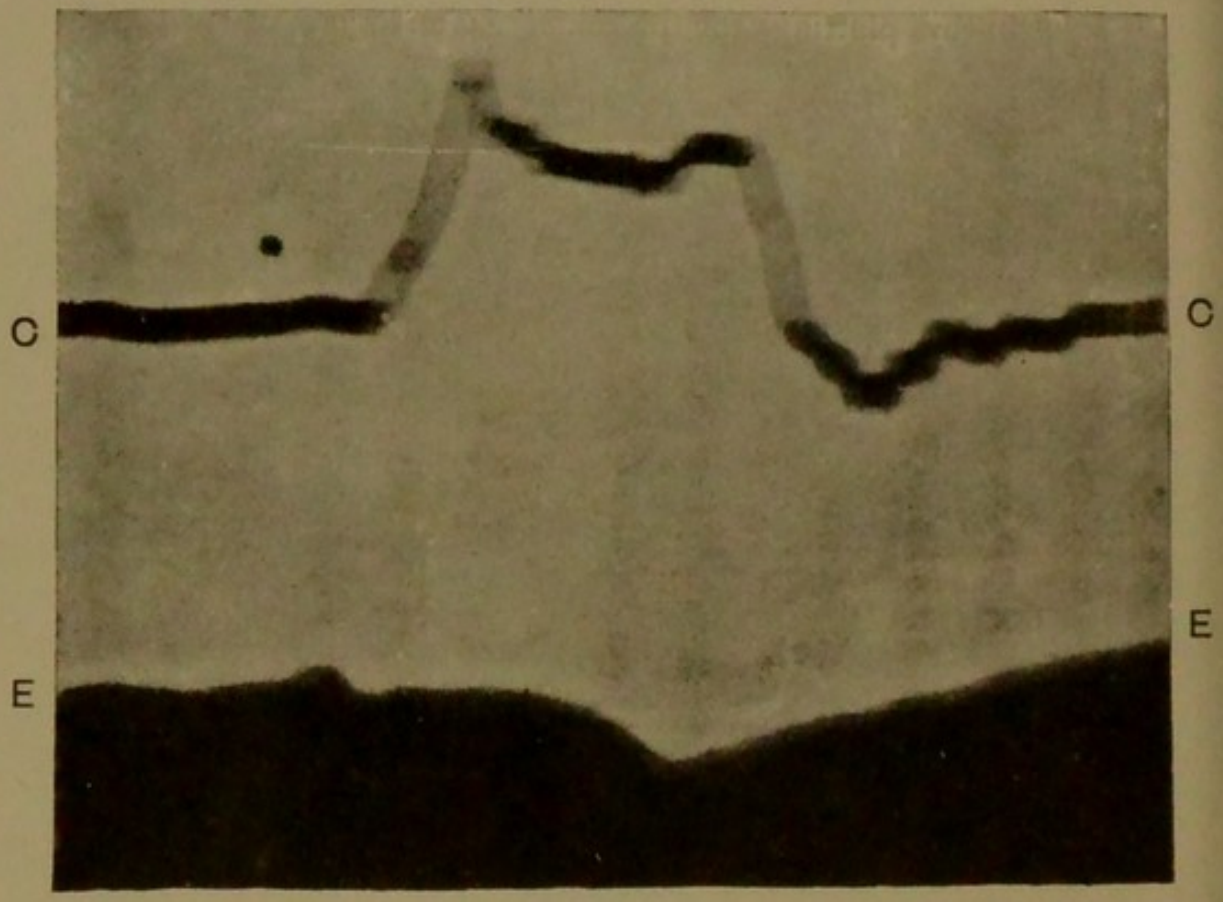


FIG. 54.—Reproduction of the Electrocardiogram alluded to in the footnote to page 12.

The line E E is formed by the photographed shadow of the column of mercury of a capillary electrometer, the two poles of which were connected with the mouth (= Base) and the left foot (= Apex). In this case A was connected to mercury, B to sulphuric acid. In Fig. 2, p. 11, and in Fig. 4, p. 15, A was to sulphuric acid, B to mercury.

The line C C is a simultaneous record of a cardiograph by which the mechanical movement of the heart was registered. (*Phil. Trans. R. S.*, vol. 180, 1899, B., p. 190.)

(Note 3, p. 54.) Sensation y increases arithmetically, while stimulation x increases geometrically. The equation to the curve expressing their ratio is—

$$x = a^y, \qquad \text{or } y = \log_a x,$$

i. e. the curve is logarithmic ; the sensation y varies as the logarithm of the stimulus x. This is Weber's law.

Fechner's formula is—

$$y = k(\log x - \log x_0)$$

where y is the sensation, k an experimental constant (differing with the nature of the sense-organ), x the stimulus, and x_0 the liminal intensity (Reizschwelle).

(Note 4, p. 57.) In relation to the sequence ABC one asks himself whether the "lost time" between A and C of a nervous reaction occurs between A and B or between B and C. In all probability it is between A and B. Dr. Veley gives the following example of such delay, viz. in a chemical reaction of the type

$$AB + CD = ABCD = AD + BC$$

there is a delay during the induction period by reason of the formation of the intermediate compound ABCD ; once started the rate of change becomes independent of the intermediate state ABCD (Bunsen and Roscoe, *Phil. Trans.*, 1857, vol. 147, p. 355 ; 1859, vol. 148, p. 879).

A mixture of H and Cl kept in dark, then exposed to light. The combination proceeds slowly at first until a maximum is reached, after which the rate decreases uniformly. This is sometimes referred to as the "Draper effect" (Hell and Urech, *Ber. d. D. Chem. Ges.*, 1880, vol. 13, p. 531).

Taking another case, that of the action of a drug upon muscular contraction, we find a sigmoid curve as the expression of the rate of chemical action of the drug upon the muscle.

(Note 5, p. 89.) I was once tempted to undertake a study of the maturation of fruits, by the blaze-test and by conductivity changes. I made a few experiments on peas and grapes, ripe and unripe. These included conductivity tests, and drew my attention to plant juices, *i. e.* of oranges, lemons and grapes, and to the variation of electrolytes, *e. g.* acids, in the course of maturation. The conductivity problem in connection with vegetable tissues is briefly considered in a paper published in the *Transactions of the*

Linnæan Society, entitled "A Week's Holiday at the Seaside with a Galvanometer and some Plants." I believe the subject to be one that would well repay further study.

Green leaves turn yellow, red or brown when they die, and cease to give any electrical response. Laurel leaves—as is well known to entomologists—give off hydrocyanic acid as they die. Their death is accelerated by anæsthetic vapours, and the changes taking place under the influence of such vapours are shown (1) by the progressive change of colour; (2) by the evolution of hydrocyanic acid; (3) by the abolition of the electrical response. I have to thank Dr. E. F. Armstrong for showing me how to follow the evolution of hydrocyanic acid by means of picrate of soda test papers (Guignard's test). The comparison by this means of the relative powers of alcohol, ether and chloroform affords a very striking experiment.

Four similar laurel leaves (*Prunus Lauro-cerasus*) are enclosed in four test-tubes containing respectively a few drops of (1) water, (2) chloroform, (3) ether, (4) alcohol. Each tube also contains a slip of picric test paper.

At the end of a few minutes, sooner at high than at low temperature, the test papers, first in 3 then in 2, begin to blush. At the end of a few hours it will be seen that the test paper in No. 1 has not altered, while those in the other three tubes give more or less evidence of an evolution of hydrocyanic acid under the influence of the anæsthetic vapours. The evolution is greatest in No. 2, from the chloroformed leaf, less in No. 3 from the etherised leaf, least in No. 4 from the alcoholised leaf. At the end of twenty-four hours the colours of the four test papers are —No. 1, unaltered light yellow; No. 2, deep red or brown; No. 3, distinctly red; No. 4, faintly red or orange.

The colours of the four leaves are altered correspondingly. No. 1, the witness leaf, is green; No. 2 is completely brown; No. 3 is green-brown; No. 4 is olive-green. Nos. 1 and 4 give a normal electrical response; Nos. 2 and 3 give no response. The evolution of HCN, which is due to the action of an enzyme (*Emulsine*) upon a glucoside (*Prulaurasin*), appears to be a post-mortem phenomenon that persists in the leaf for days. It does not come off with Bay leaves (*Laurus nobilis*), nor with the leaves of Portuguese laurel (*Cerasus lusitanica*), nor with those of *Orcuba japonica*. The effect of petrol vapour is about equal to that of alcohol. I have not followed the matter into further detail as regards the temporary or permanent nature of the alterations, nor have I applied this obviously convenient method of estimating the relative toxicities of other poisons.

(Note 6, p. 90.) Prof. Johnson tells me that it was recently suggested in Germany (by Dr. Muth at the Strassburg meeting of the Vereinigung für angewandte Botanik) that the blaze-test might be applied to the case of the *hard* seeds of clover, lupine, etc., which may take several years to germinate, and cannot therefore be pronounced to be dead because they have failed to germinate in a few days.

The blaze-current is the "first sign of life" as well as the "last sign of life." The experiments on seeds mentioned earlier in the lecture are proof of this: a pea or bean manifests the sign after an hour's immersion in warm water. A developing hen's egg manifests it as soon as a blastodermic membrane is formed ("On the Blaze-currents of the Incubated Hen's Egg," *Proc. R. S.*, vol. 71, p. 184, 1902). See also "Le dernier signe de Vie," *Comptes Rendus de l'Académie des Sciences*, September 3, 1900, and March 6, 1901; "Le premier signe de Vie," *Ibid.*, December 24, 1900.

(Note 7, p. 99.) *Temperature and pressure corrections in chloroform estimation by densimetry.* More exact numbers than those quoted in the text are—

1000 c.c. of chloroform vapour at 0° and 760 mm. Hg	= 5·333	grammes
1000 c.c. of atmospheric air at 0° and 760 mm. Hg	= 1·288	,,
Difference	= 4·045	,,

My correction formula is as follows—

$$\text{Log } P = 1{\cdot}8377 + \log m - \log v + \log T - \log B,$$

where P is the percentage required,
m the observed increment of weight in milligrammes,
v the volume of the bulb in cubic centimetres,
T the absolute temperature in degrees centigrade,
B the barometric pressure in millimetres of mercury.

Example.—From an observation taken at Johannesberg, South Africa, with a bulb of 260 c.c., the barometer standing at 600 mm. Hg, and the thermometer at 25°, the densimetric increment was observed to be 34 milligrammes. What was the chloroform percentage P?

Answer—

$$\text{Log } P = 1{\cdot}8377 + \log 34 - \log 260 + \log 298 - \log 600$$
$$= 0{\cdot}6504$$
$$\therefore P = 4{\cdot}471$$

(Note 8, p. 106.) On July 12, 1909, a death took place under the influence of carbon tetrachloride (CCl_4) under the following circumstances. A young lady, who according to the evidence of all her intimate friends and relatives had always enjoyed excellent health, went to a hairdresser's to have her hair washed. She was persuaded by the assistant to undergo what was termed a "dry shampoo," although she was informed by the assistant that it might make her feel ill. After the operation had been conducted in the usual way for about two minutes, the lady leant forward and collapsed. She was laid on the floor, and ceased breathing two or three minutes after. Artificial respiration and other measures were applied with no avail.

At the inquest the medical evidence was to the effect that death was due to sudden heart failure, possibly in consequence of *status lymphaticus*, possibly accelerated by inhaling carbon tetrachloride.

The verdict was: Accidental death, accelerated by the fumes of carbon tetrachloride, with a rider to the effect that —— were not justified in employing unskilled operators in performing this dangerous operation.

In the *Lancet* of August 7 I published a note on the relative toxicity of chloroform ($CHCl_3$) and of carbon tetrachloride (CCl_4), in which I showed that carbon tetrachloride is considerably more poisonous than chloroform, and that the incriminated hair wash, which, according to Dr. Veley's analysis, contained 93 per 100 of carbon tetrachloride, is still more poisonous.

On August 25 a prosecution was instituted by the Director of Public Prosecutions on the charge of manslaughter. The charge was withdrawn, on the undertaking of the incriminated firm that the preparation was never again to be used in their establishment. The prosecution was held to have served the purpose for which it was intended, in bringing to the notice of the public the dangerous nature of the dry shampoo when carbon tetrachloride was used; and to give a severe warning against the use of this substance by any other persons for that purpose, since if any future deaths occurred a serious charge would of necessity be instituted.

It is to be hoped that the inquiry conducted by the Home Office may be the means of preventing the recurrence of such

fatalities, and lead to a less dangerous laxity in the regular administration of chloroform.

(Note 9.) *Quantitative estimation of chloroform in the blood post-mortem.*—For medico-legal purposes the procedure as detailed by Nicloux can be followed:—The blood (20 c.c. taken by pipette or syringe from the right auricle or venæ cavæ) is at once shaken up in a 4 oz. stoppered bottle with 80 c.c. of alcohol acidified by 5 c.c. of a 5 per cent. solution of tartaric acid. The mixture is transferred to a flask and distilled (as ammonia is treated for N determinations by the Kjeldahl method). The distillate is collected in a graduated vessel containing already 10 c.c. of alcohol so as to cover the delivery tube. The distillate consists of alcohol and chloroform, and when the level is at 50 c.c. contains the whole of the chloroform present in the original fluid. It is now boiled for an hour with the addition of 10 c.c. of a 10 per cent. solution of potash (or preferably caustic soda made from sodium, which is easier to obtain chlorine free) in alcohol to form potassium chloride.

The resultant potassium chloride is titrated as follows:—Two drops of a 3 per cent. alcoholic solution of phenol-phthalein are added to the cooled distillate, excess of alkali having been neutralized by nitric acid, and a little calcium carbonate being finally added to ensure complete neutralization. Two c.c. of a 5 per cent. neutral solution of potassium chromate are added to the liquid. The final titration is made with a 4·268 per cent. solution of silver nitrate, of which 1 c.c. corresponds to 1 millligramme of chloroform. The turning-point from yellow is best appreciated by using as a term of comparison a similar flask in which the chlorides are in slight excess, so that the colour is frankly yellow. The first appearance of silver chromate indicative of the end-point of the silver chloride is taken as being the permanent darkening of tint visible when the flask is shaken. Two drops of silver nitrate (at 20 drops to the 1 c.c. = 0·1 = $\frac{1}{10}$th milligramme of chloroform) are sufficient to give a clear end-point.

With 20 c.c. of blood 10 milligrammes of chloroform (= 50 milligrammes per 100 c.c.) are indicated by 10 c.c. of silver solution.

If the turning-point requires more than 10 c.c. of silver nitrate there has been excess of chloroform in the blood. The error is always on the side of too low an estimate, especially if the blood has clotted before it is collected, or if it has become diluted by serum or other animal fluid.

The end-point by this method is not easy to settle precisely without considerable previous experience.

To any one who prefers, therefore, to estimate chlorides by Volhardt's method it is obviously open to evaporate off the alcohol after treatment with potash, take up the residue in water, and proceed from this point in the usual way :—

"A known volume of N/10 silver in excess is added, having previously acidified the liquid with nitric acid ; the mixture is well stirred, and the supernatant liquid filtered off through a small filter, the chloride well washed, and to the filtrate and washings, 5 c.c. of ferric indicator and the same volume of nitric acid are added. The flask is then brought under the thiocyanate burette, and the solution delivered in with a constant gentle movement of the liquid until a permanent light-brown colour appears. If the silver chloride is not removed from the liquid previous to titration a serious error may occur, owing to the ready solubility of the chloride in the thiocyanate solution." (Sutton, *Volumetric Analysis*, 9th ed., p. 172.)

N.B.—It is important that all reagents used for these determinations should be ascertained to be free from chlorides.

(Note 10.) *A new method for the quantitative estimation of small amounts of hydrocyanic acid.*

The study of hydrocyanic acid evolved by laurel leaves has led me to work out a method for its quantitative estimation that is generally applicable to animal as well as vegetable tissues. The method is colorimetric, and depends on the reaction between cyanides and picric acid, which was first studied by Hlasiwetz (Liebig's "Annalen," **110**. 289 (1859)), and as mentioned in Note 5, applied by Guignard to the detection of minute quantities of hydrocyanic acid.

A colour-scale is prepared by mixing equal volumes of a recently-titrated solution of 1/1000 hydrocyanic acid and of picrate mixture (equal volumes of 0·5/100 picric acid and 5/100 sodium carbonate). From this stock solution, left for 24 hours at 40°, a colour-scale is prepared by further dilution with picrate, to contain 1, 2, 3 . . . . etc. parts of HCN per million, of tints T1, T2, T3, etc.

The estimation of the amount of HCN in any given tissue or liquid is made by matching the tint of the liquid, or of a distillate into picrate mixture, with that of the colour-scale.

Thus, *e. g.*, if the tint of a distillate from 10 c.c. of blood (dil. × 5) into 25 c.c. of picrate is found to be T5, and the volume of picrate + distillate is 40 c.c., the amount of HCN in the distillate = 5 × 40 millionths gramme, *i. e.* 0·000200. The distillate should be left for a few hours in an incubator at 40°

to bring out the full tint. A second distillate may be taken to show whether or no the first distillate has taken over all the HCN present.

The scope of this method may be illustrated by an actual experiment showing the amounts of HCN so found in the blood, brain, heart, and skeletal muscle of an animal poisoned by hydrocyanic acid, and the time *post-mortem* when the poison can still be found and estimated.

Experiment 1. *Cat*—2·4 kilos—death by intravenous injection of 100 milligrammes HCN. Distillates into 25 c.c. picrate from 10 grammes brain, and from 10 grammes blood.

16 hours *p.-m.*
Brain gave T60 in 33 c.c. = 0·001980 grm. HCN per 10 grms.
Blood „ T24 in 32 c.c. = 0·000768 „ „ „

3 days *p.-m.*
Brain gave T30 in 30 c.c. = 0·000900 „ „ „
Blood „ T10 in 31 c.c. = 0·000310 „ „ „

7 days *p.-m.*
Brain gave T10 in 30 c.c. = 0·000300 „ „ „

Experiment 2. *Cat*—3 kilos—death by intravenous injection of 50 milligrammes HCN. Distillates as before, and taken the same day.

Blood gave T10 in 30 c.c. = 0·000300 grm. HCN per 10 grms.
Brain „ T20 in 31 c.c. = 0·000620 „ „ „
Heart „ T25 in 31 c.c. = 0·000775 „ „ „
Muscle „ T3·5 in 31 c.c. = 0·000108 „ „ „

Experiment 3. *Cat*—2·2 kilos—death by intravenous injection of 5 milligrammes NaCN (= 2·6 mgrms. CN). Distillates into 10 c.c. of picrate, taken on the same day.

Blood gave T1·5 in 20 c.c. = 0·000030 grm. HCN per 10 grms.
Brain „ T4·5 in 20 c.c. = 0·000090 „ „ „
Heart „ T4·5 in 20 c.c. = 0·000090 „ „ „
Muscle „ T0 in 20 c.c. = nil.

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