BRAIN.

PART I., 1900.

Original Articles and Clinical Cases.

ON THE EXCITABILITY OF NERVOUS MATTER, WITH ESPECIAL REFERENCE TO THE RETINA.¹

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I HAVE not failed to pass through the preparatory searchings of mind incidental to the delivery of a presidential address, nor to sacrifice to custom by the deliberate writing of a bulky manuscript heavily charged with midnight reflections. But one outcome of those reflections has been an intimate conviction that such deliberate writing is fitted only for the deliberate reading of the fireside, and that it would be impossible for me, within reasonable limits of time, to make my meaning fully clear, by reason of the detail in which it has become enveloped. I have therefore thought preferable to cut myself adrift from the manifold detail of written thought, and endeavour, however lamely and ungrammatically, to at least indicate to you what are the chief new facts that I am selecting to lay before you, and what is the vein of sense which to my mind renders them of neurological value.

¹ Presidential Address to the Neurological Society, February 8, 1900.

My contribution to our common theme is coloured from the laboratory—which, however, will not be accounted to me for unrighteousness in a Society whose distinguishing characteristic it is that it forms a meeting place of complementary interests—from the domain of the laboratory as well as from the hospital—the two chief colours, so to speak, that together make for the neurologist the white light of his knowledge. Nor—to continue the analogy—shall I be unmindful of a third colour by which the triangle of interests is completed in our Society, and I shall try to indicate in the course of my address points of contact with psychological doctrine, of some of the dry facts that belong in first place to physiological analysis.

Let me briefly summarise the subject-matter that I hope to review this evening. I divide it into three chapters, and shall hope under each of these three heads to clearly develop and fix at least one idea of elementary neurological interest.

In Chapter I. I shall briefly refer to a method of procedure, and insist upon the principle that systematic observation of the electrical signs of life yields valuable information.

In Chapter II. I shall consider at some length the constructive and disruptive phenomena of which nervous matter is the seat. I shall do this with particular reference to electrical changes produced in the retina by light. I shall briefly describe those changes, and derive from them the conclusion that light excites in the retina a double process of simultaneous decomposition and recombination; and in conclusion to this chapter I shall take occasion to describe the specific action of protoveratrine upon medullated nerve, viz., an abolition of the positive reaction after action. Incidentally to this matter I shall also refer to the great exhaustibility of non-medullated nerve, and to the slight exhaustibility of the retina as compared with the apparent inexhaustibility of medullated nerve-fibres.

Chapter III. will consist in the consideration of what I term the "law of response," in so far as it can be ascertained by study of the quantitative relations between physical exciting cause and physiological excited effect. My special conclusion *qua* the retina will be:—that the cause-effect curve is an S-shaped or sigmoid curve. My general argument will be:—that a sigmoid curve expresses the ratio between physical stimulus and physiological effect, as well as between physical stimulus and psychological effect.

I.—THE ELECTRICAL SIGN OF LIFE.

Living nervous matter—all living matter indeed—is "excitable" and responds to its "call-from-without" by some form of movement—chemical movement, mechanical movement, electrical movement. An animal gives sign of life by moving. An isolated muscle gives sign of life by contracting when stimulated, and we are able by more or less refined methods to show that such contraction is accompanied by physico-chemical changes—production of acid, evolution of carbon dioxide, rise of temperature, electro-motive action. An ordinary nerve, normally connected with its terminal organs, gives sign of life by means of muscle, which by direct or reflex path is set in motion when the nerve-trunk is stimulated. But such nerve separated from its natural termini, isolated from the rest of the organism, gives no sign of life when excited, either in the shape of chemical or of thermic changes, and it is only by means of an electrical change that we can ascertain whether or no it is alive. The eye—the retina—is known to us as a living organ in our own persons when we see an external object. By various devices of the laboratory we measure quantities of stimulant light and differences of excited sensation. The isolated organ—an entire eyeball, or its isolated retina—is best known to be alive or not by means of its electrical response or silence when it is put to the question by its natural stimulus light.

In the three cases named the most general and most delicate sign of life is then the electrical response, and I shall hope to show that the electrical signs of life studied

FIGS. 1 AND 2.

Simultaneous record of a series of muscular contractions and of the corresponding electrical responses.

The muscle (frog's gastrocnemius) connected to an isometric myograph (record A), and led off to a galvanograph (record B), is excited by tetanisation of the sciatic nerve at one minute intervals. Each period of tetanisation lasts six seconds.

and measured in the laboratory upon these three organs afford very definite contribution to fundamental principles of neurology.

I do not now propose to dwell upon either nerve or muscle. Let me, however—towards establishing in your judgment the general credit of the electrical sign of life—make very brief allusion to experiments upon these two tissues.

To muscle I shall appeal solely to make good the preliminary position. Compare, *e.g.*, these two simultaneous records—(a) of muscular contractions, (b) of the electrical responses belonging to the contractions. The electrical effects are to all intents and purposes a replica of the contractions; and if you admit contraction to be valid physiological testimony, you must admit the electrical response to be at least equally valid. The parallelism—as regards fatigue of the end-plate in this case—between the two kinds of record is close, not indeed quite perfect; but of the two versions I should say that the galvanometer gives a rather more faithful report than does the myograph as regards the quantity of chemical change underlying the visible mechanical change.

In the case of nerve, which has no mechanical expression of itself otherwise than by means of muscle, we may, and indeed must, rely upon the galvanometer alone for information as to its physiological state. And nerve—the most hopeless tissue to investigate by way of the indications of muscle, hopeless because nerve is so tough and its terminals are so tender—is an almost ideal sample of living matter upon which to test the comparative effects of all manner of reagents, when the galvanometer is made to be its organ of expression. For we have in our hands a living tissue, absolutely isolated from all other tissues, responding with unfailing regularity so long as nothing more is done to it, and therefore informing us whether or no any given experimental modification affects it. I will content myself by exhibiting to you two typical nerve-records illustrating what I have already on previous occasions at the Society claimed as the distinctive excellence of the method, *viz.*, the clearness of its results. Figs. 3 and 4 are the records of two experiments in which the effects of two gases are tested upon an isolated nerve, their incidence being signalled by the vertical dark

bar. There is no doubtful or obscure result. The gas A had no action. The gas B had an evident action.

A

B

FIGS. 3 AND 4.

Two records of series of electrical responses of nerve, upon which effects of gases are tested. Excitation by tetanisation for 7.5 secs. at one minute intervals. The time during which the nerve is submitted to the influence of the gas is signalled by a vertical dark bar across the record. Gas A is an indifferent gas. Gas B is an anæsthetic gas.

N.B.—The scale in these and other records gives the approximate voltage of deflections.

II.—CONSTRUCTIVE AND DISRUPTIVE MOVEMENT.

Let us take as a point of departure "the axiom of general physiology," to which we all subscribe.

Living nervous matter—all living matter—is the seat of two opposite tendencies, integrative and disintegrative, synthetic and analytic, centripetal and centrifugal, constructive and disruptive, anabolic and katabolic, positive and negative. Each act of life is act of death. A muscle by the act of contraction, a nerve-cell by the act of explosion, manifests energy, expends stored matter, undergoes fatigue, and requires to be replenished by the converse act of nutrition. Living tissue, inasmuch as it is living, is also dying tissue, ceaselessly evolving energy, ceaselessly "re-storing" energy.

FIG. 5.

To show direction of currents in muscle, nerve, and eyeball. Arrows at top of figure indicate direction of normal current ("current of injury"). Arrows below indicate direction of electrical response to excitation ("current of action").

The double chemical current of which living matter is the centre, manifests itself by actual chemical and structural consequences when it has been sufficiently intense or sufficiently prolonged. Its weakest and briefest pulsations are manifested by electrical changes.

Taking as our line of departure, or zero level, the low-grade continuous chemical change normal in the unexcited state of living tissue—muscle, for example—we have a greater electro-motive action with greater activity of muscle, a lesser electro-motive action with lesser activity. There is

no difference of chemical and electrical state between any two points of an ideally normal uniform muscle—all points are equally alive. If one of the two points be positively active, it will be positively electro-motive. If one of the points be negatively active, it will be negatively electro-motive.

Living muscle—or living nervous matter—or, indeed, any living matter—is excitable, and the most delicate physical sign of that excitability is electromobility, viz., the capacity of manifesting an electrical change in response to excitation. Such electrical change in response to excitation may be positive or negative, positive with augmented disintegration, negative with augmented reintegration.

A muscle, a nerve, an eyeball connected with a galvanometer, as shown in these three sketches, manifests current which we may designate as being upwards (in the tissue) or to the right (through the galvanometer), or positive.

This upward current is due in each case to electro-motive action at the point of injury, and gradually subsides—most rapidly in the case of the eyeball, which is apt to exhibit soon after excision a reversed or downward current.

During excitation the upward current undergoes a diminution in the case of muscle or of nerve, an augmentation in the case of the eyeball.

I shall not dwell on the first two cases, they are only presented as affording standards of comparison with the third case, that of the eyeball.

There are two obvious points in the comparison :—

(1) Fatigue, as evidenced by the diminishing maximal effects of a series of maximal excitations, most obvious in the case of muscle, not obvious at all in the case of nerve, is only moderately well marked in the case of the eyeball.

(2) The effects of excitation are negative in the case of muscle and nerve, positive in the case of the eyeball.

Both these points require some comment.

(1) The conditions of observation in the three cases are not strictly identical. In the first two cases the excitation has been electrical, in the third it has been a stimulation by light. I have not yet succeeded in obtaining for comparison

FIGS. 6, 7, AND 8.

Currents of action of nerve, of muscle, and of retina.

In each case the excitation lasts for one minute, and the subsequent period of rest for two minutes. There are five periods of excitation in each series. The nerve is excited by tetanising shocks; the muscle is excited by tetanising shocks of its nerve; the retina is excited by exposure to candle-light.

The nerve record exhibits a series of undiminishing negative variations.

The muscle record exhibits a diminishing series of negative variations.

The eye record exhibits a slightly diminishing series of positive variations.

a series of retinal responses by electrical excitation.¹ It seems to me, however, that the comparison now made is a permissible one, the retina having presented to us a series of maximal effects by maximal stimulation by light. Such being the case, we may comment upon the remarkable endurance of the response, and express the opinion that such endurance is due not to insignificant chemical disintegration during activity, but to considerable and effective chemical reintegration during repose, and, it may be, during activity itself. I am of the opinion, on grounds that I hope shortly to make clear, that reintegration of retinal matter sensitive to light, goes on during its disintegration by light, as well as during darkness—that during activity retinal exhaustion is prevented by retinal invigoration. I shall return to this point presently.

(2) The fact that the retinal response is positive, whereas the responses of muscle and of nerve are negative (to the original upward current of rest of fig. 5), has not quite the simple significance that might at first sight be attributed to it. The actual direction of current of rest in the eyeball is unessential to the direction of the current of illumination; the former may be positive or negative, whereas the latter, which is the essentially interesting effect, is in general positive. It is advisable for any clear understanding to consider the latter without any reference to the former, and to realise its direction through the layers of the retina. If we consider an eyeball in its natural position, with cornea facing the sky and optic nerve stump to the ground, the direction of our current is upwards from the choroidal or pigment layer of the retina to its vitreous or nerve-fibre layer, and to be represented by an arrow pointing upwards from fundus to cornea—as we fancy we look at things—and thereafter through the galvanometer completing circuit from cornea to fundus. I usually take as my working mnemonic in the laboratory that the retinal response of an eye looking at the galvanometer “looks through” the latter. Where shall we look for the motive force driving our imaginary arrow? I think at the rod and cone layer of

¹ Note 8, p. 35.

the retina, where therefore you may picture as placed the tail of the arrow, the part to which the tense bowstring of photo-excitability is applied and liberated by the stimulus of light. But let me repeat that we are to conceive that two simultaneous and opposite movements are promoted in the retina by light—the winding-up process by which potential energy is stored, the running-down process by which active energy is liberated.

I alluded to the grounds on which this view is based ; let me now briefly expose these grounds.

The positive electrical effect of retinal illumination is assuredly not a single simple phenomenon, but a compound effect—the resultant of simultaneous and antagonistic forces. Being antagonistic, such forces must be conceived as two in number, or at least in two opposite camps if the components ultimately discovered should prove to be more than two. But however numerous such components might prove to be, they could not take effect otherwise than in one or other of two directions, which we shall therefore distinguish as positive and negative.

The signs by which we may recognise that the positive electrical effect of retinal illumination is double, are apparent at the commencement and at the end of prolonged illumination—at “make” and at “break” of light.

The main or principal effect *during* illumination is positive, and this positive effect gradually subsides during obscurity. Usually the initial effect at the commencement of illumination, *i.e.*, at *make* of light, is positive, but occasionally it is distinctly negative, and sometimes it is doubtful to an observer whether the very first motion of the galvanometer spot is negative or positive ; sometimes again it is distinctly positive, then negative, before passing into the enduring positive position it takes up during illumination.

At the end of illumination the subsidence of the positive deflection is always preceded by a more or less well-marked sharp positive augmentation, *i.e.*, at *break* of light there is a sharp augmentation of the positive deflection during light, followed by gradual subsidence to the obscurity level.

One's first thought in presence of this somewhat puzzling break effect, is that the main positive effect during illumination may be a sign of pigment activity, while the terminal positive effect at break of light may be due to a movement of the cones. But on this view it is difficult to account for the fact that the terminal effect, if due to relaxation of cones, has not always its distinct initial counterpart at make of light by reason of a contraction of cones. I therefore hesitate to offer this in explanation of the facts, and shall content myself with the demonstration of the presence of two simultaneous and opposite effects,

FIG. 9.

Eyeball of the second stage with a "period of hesitation" lasting five seconds.

without committing myself to an assertion that such opposite effects have their seat in the same or in different retinal elements.

The lost time of these make and break effects, more especially of the former, *i.e.*, the time elapsing between the commencement of illumination and the commencement of deflection, is highly significant of the double nature of the chemical change of which the electrical change is the outward and visible sign.

As regards the make effect in particular, or rather the

practically simultaneous make-break effect of a flash light, the interval between stimulus and deflection is physiologically enormous, obvious to simple observation as quite a long pause, and not requiring therefore a very rapidly travelling plate for its photographic registration.

We evidently have to do, not with a simple period of latency—such physiological inertia in the case of the retina is simply incredible—but with what I shall characterise as a period of hesitation, during which a tug-of-war, so to say,

FIG. 10.

An old record of the retinal response to light (June 4, 1895; Candle at 2 feet = 25 units), which, although not of the usual type, I then regarded as being normal. In a sense it is so, but only for an eyeball in the second stage, as described in the text.

is taking place in the retina between two opposite forces or processes, positive and negative, that for a period counterbalance each other in the circuit.

A similar if less pronounced opposition of forces occurs at the end of illumination, when the two forces cease to act. But whereas we must suppose that at make of light, both forces commence to be evolved at almost equal rates, and that during light the positive force is the stronger, we must admit that at break of light, negative ceases more

suddenly than positive, so that a short positive *plus* precedes the more gradual positive *minus*. And if from any cause there should have been during the period of hesitation at make of light a sufficiently marked superiority of negative over positive, then we shall witness at make of light a distinct negative effect preliminary to the main positive effect—as shown in fig. 10.

The record, which was taken in July, 1895, was obtained on an eyeball in the second or transitional state, and Professor Kühne, when I showed it to him, recognised at once that it was the response of a partially-injured eyeball. The hint was not lost upon me. On returning to the subject last year I paid particular attention to the transitional types that are observed. And since I have mentioned Kühne's name in this connection to acknowledge a valuable hint, I should like to take the opportunity of showing you how closely some of my photographic records of 1899 reproduce the plotted curves of Kühne and Steiner of 1881. I have confronted in the two halves of fig. 11 Kühne and Steiner's fig. 1, which they give as representing the usual course of events in the isolated retina, and one of my own records of a response of an eyeball in the second stage. The similarity is sufficiently obvious.

That this is a reasonably probable view to take of the case is confirmed by the alterations of effect taking place in an eyeball accidentally mishandled, or left to become partially dry upon the leading off electrodes. From the freshly-prepared state, with an eyeball at its best, to the moribund state with an eyeball at its worst, I distinguish three stages.

In Stage I. the deflection at make of light is at once positive, the deflection during illumination is positive and increasing or stable; the deflection at break of light is positive and small, followed by gradual decrease of the main positive deflection to the normal obscurity level.

With lapse of time the main positive effect is less and less sustained during illumination, and the terminal deflection at break is relatively large. The deflection at make of light becomes "hesitant," being sometimes frankly

FIG. 11.

Comparison between Fig. 1 of Kühne and Steiner's second paper on retinal currents (1881) and a record of retinal response of the second stage, as described in the text.

FIGS. 12, 13, AND 14.

Electrical responses to illumination of the retina in the three stages described in the text.

(I.) Fresh eyeball. Considerable and augmenting positive effect. Small terminal positive increment.

(II.) Eyeball about six hours after excision. Initial positive effect followed by prolonged negative effect. Large terminal positive deflection.

(III.) Eyeball about twenty-four hours after excision. Clear negative effect during illumination.

In each case stimulation is made by exposure lasting one minute to a standard candle 2 feet from the eyeball.

(Fig. 8 is the continuation of Fig. 12, recorded from the same eyeball on a more slowly travelling plate.)

negative, sometimes positive with negative interruption, sometimes positive after a long period of hesitation.

In Stage II. the main positive deflection has disappeared, the state during illumination being neutral or actually negative. At make of light the deflection is positive, and markedly "hesitant." The terminal deflection at break of light is positive and large, being, in fact, the most prominent feature of the sequence.

In Stage III. the deflection is negative throughout illumination; at make the deflection is frankly negative, during light it is decreasingly negative; at break the deflection is positive, and the spot returns to its normal level of obscurity.

An even cursory review of these three stages, taken in conjunction with the peculiar period of hesitation at make of light, must reinforce the view that we are in presence of a double process, and that the dominantly positive effect of Stage I. has latent in it the opposite negative effect that is wholly unmasked in Stage III.

I have sought in many ways to separately influence the positive and negative effects—by drugs, by strong electrical currents, by raised temperature, by increased eyeball tension—acting on the supposition that by partial injury I might be able to, so to speak, wipe out the presumably more delicate process of constitution, and thus unmask the more enduring process of destitution. I find that the best and almost unfailing means of doing this is to partially injure the retina by compression of the eyeball. For an effective lecture demonstration, a fresh eyeball, giving the regular positive effect on illumination, may be taken off the electrodes, moderately compressed and rolled between the fingers, and replaced upon the electrodes; the effect of illumination on this massaged eyeball will almost certainly be negative.

Colour antagonism?

One may hardly be expected to make even the most cursory survey of positive and negative retinal changes without allusion to the comparative effects of the several

colours that make up white light—with reference of course to the well-known antagonism theory of Hering, white *v.* black, red *v.* green, yellow *v.* blue, which has played such a prominent part in the literature of colour-vision. We have seen that there is a very clear antithesis as regards the retinal effects of light and darkness, so that we might perhaps say that white and black are antagonists, and that white provokes an action while black promotes an opposed reaction. Can any similar antithesis be recognised between the two “dissimilative” colours red and yellow and the two “assimilative” colours green and blue, which, on the antagonism theory, are regarded as promoting opposite chemical changes in the retina?

On trial of this point we find in all cases that different colours give rise to electrical effects in one direction, though of varying magnitude. The order of efficacy in my own trials, made with carefully selected coloured glasses, has been:—red, blue, green, yellow, white, *i.e.*, in a sense that is obviously governed by luminosity. To quote an instance, the deflections were

With Red	..	..	..	..	..	..	..	+	4
Blue	..	..	..	..	..	..	..	+	9
Green	..	..	..	..	..	..	..	+	12
Yellow	..	..	..	..	..	..	..	+	16
White	..	..	..	..	..	..	..	+	33

Stimulation at 25 units. Illumination for 6 seconds at 1 minute intervals.

But we at once object that a possible opposition between the purely chromatic constituents has, perhaps, been masked by the white-valency common to all the colours, or by white light passing through the imperfect colour filters.

We therefore make two further series of trials (1) to learn whether the joint effect of two opposed colours is greater or smaller than their separate effects; and (2) to learn whether the separate effects of any two opposed colours are equally or unequally altered when the retina has been submitted to prolonged modification by one of the two colours.

I find (1) that taking two very weak colour stimuli, *e.g.*, red and green, the conjoint effect of both stimuli is always

greater than either of the separate effects, and not far short of their sum ; (2) that a retina subsequent *e.g.*, to prolonged green stimulation or to prolonged red stimulation, exhibits equal fatigue to green and to red stimuli.

Here are two representative experiments—

I.

Red alone	..	..	..	..	..	+	5
Green alone	..	..	..	..	..	+	10
Red + Green	..	..	..	..	..	+	14
White	..	..	..	..	..	+	40

Stimulation at $\frac{1}{4}$ unit.

II.

Red	..	..	..	..	..	..	+	21
Green	..	..	..	..	..	..	+	28

Ten minutes' exposure to Green.

Red	..	..	..	..	..	..	+	16
Green	..	..	..	..	..	..	+	24

Ten minutes' exposure to Green.

Green	..	..	..	..	..	..	+	22
Red	..	..	..	..	..	..	+	15

Ten minutes' exposure to Red.

Green	..	..	..	..	..	..	+	20
Red	..	..	..	..	..	..	+	12

Ten minutes' exposure to Red.

Red	..	..	..	..	..	..	+	8
Green	..	..	..	..	..	..	+	18

Stimulation at 100 units. Lasting 10 seconds.

But for my own part, I must confess that I do not attach much value to these colour experiments. They are made upon the frog's retina ; we have no reason to think that the frog is at all a judge of colour ; the results show at most that the hypothetical chemical antagonism of colours is certainly not any deep-seated physiological anti-thesis pertaining to all retinal matter "excitable" by light. The psychologist remains as free as ever to believe or not to believe that the perception of colour by the human brain is three dimensional, and depends upon disintegration-cum-reintegration of a white-black substance, and of a red-green substance, and of a yellow-blue substance. But this to my

mind is a psychological chemistry, and I do not wish to wander too far afield from a physiological base.

Let me bring this chapter to a close by referring briefly to the positive and negative electrical effects that are manifested by ordinary nerve. The three stages just described as regards retinal effects, and the very probable double character of such effects, recall to mind the somewhat similar series of effects in freshly isolated dying nerve. Only whereas the three stages that I described in the case of nerve refer to electrical effects of electrical excitation, the retinal series refer to electrical effects of luminous stimulation.

The electrical response of isolated nerve tetanised by alternating currents is with lapse of time:—(1) a simple negative effect; (2) a negative effect immediately followed by a positive after effect; (3) a positive effect. Nerve in the second stage seems to be most clearly suggestive of the operation behind the scene of two opposite processes of action and reaction, of which the prominent manifestations in this case are successive. It would appear, moreover, that there is some kind of analogy between the early positive and late negative effects in retina on the one hand, and the early negative and late positive effects in nerve on the other hand, but I should be very unwilling to speculate very far along this superficial and obvious analogy. We may, however, consent to speculate in moderation, and admit that just as in the retina there is a store of matter that is formed, and that is consumed under the excitation by light, so in nerve there is analogous stored matter formed by activity and subserving activity.

Significance of the Medullary Sheath. Fatigue of Non-Medullated Nerve.

Naked gray matter, as of a nerve centre, is very rapidly exhausted, and has to be replenished at leisure from the nutritive fluids. Protected gray matter, as the conductile axis of medullated nerve-fibre, is extraordinarily inexhaustible because its wear and tear of action is instantly effaced

by the restorative reaction of its white envelope; just as the highly mobile elements of the retinal organ, provoked to action and therefore to expense by light, are *pari passu* kept supplied and protected from exhaustion out of the store of pigment that is our visual inogen.

It is by action and reaction between core and sheath that the nerve-impulse is propagated along a medullated nerve-fibre. It is by the same action that the impulse is insulated within a definite conducting fibre. And by the same means there is secured to the essential part—the grey core—an almost instantaneous restoration of expended matter necessary to unimpaired function rapidly repeated.

Do we ask for evidence of a commerce of matter between the grey core and its white jacket of phosphorised fat? We have such evidence—and of the most cogent—in the first gross fact of Wallerian degeneration. The grey core of a nerve-fibre is the arm of a nerve-cell which is its body, and when the nerve is cut the arm degenerates away from the body. The first and most obvious change of structure takes place, not in the core itself, which was in continuity with the cell body, but in the discontinuous sheath, by which it is enveloped and nourished. The disordered nutrition of the principal part—the axis, is first visibly manifested by the superadded and subordinate part—the sheath.

If this hypothesis be well founded, we should expect that non-medullated nerve, examined as to exhaustibility, would be found to conform to the type of exhaustible muscle rather than to the type of inexhaustible nerve.

Miss Sowton, who at my request has investigated the point upon the olfactory nerve of the pike, has as a matter of fact found this to be the case.

Veratrine and Protoveratrine.

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, and causes its contraction to be extraordinarily prolonged. A veratrinised

muscle contracts vigorously but does not relax. Pure veratrine has comparatively speaking no action upon nerve.

Protoveratrine, which has recently been identified and distinguished from veratrine by Boehm, has a specific

FIGS. 15, 16, 17 AND 18.

Portions of records of ordinary muscle, of medullated nerve, and of non-medullated nerve (olfactory nerve of pike) similarly excited—to show that non-medullated nerve resembles muscle and differs from medullated nerve, as regards the manifestation of fatigue.

Fig. 18 is a similar retinal series of responses to light, exhibiting little or no sign of fatigue (retina of the third stage).

FIGS. 19 AND 20.

To illustrate the contrast between veratrine and protoveratrine.

In each case a frog has received an injection of one drop of a $\frac{1}{2}$ per 100 solution of the alkaloid (=about 0.0005 gramme, *i.e.*, a very large dose). Between $\frac{1}{2}$ and one hour later the apparently dead frogs have been pithed and a sciatic nerve of each has been removed and placed upon the electrodes.

In each case three electrical responses (at intervals of one minute to tetanisation lasting for six seconds) have been recorded.

The three veratrine responses are normal and undiminishing; each response exhibits a negative effect during excitation and a positive effect after excitation.

The three protoveratrine responses are sustained and diminishing; each response exhibits a negative effect during and after excitation.

The deflection to the left of each record is a standard deflection made by passing current from $\frac{1}{1000}$ volt through nerve and galvanometer. It serves to give the voltage scale of the nerve-responses, and shows to what extent the galvanometer is "dead-beat."

action upon nerve, and comparatively speaking no action upon muscle. It causes the negative variation of excited nerve to be extraordinarily prolonged. The fact in itself is of considerable interest, inasmuch as it is at present a solitary and very clear case of two drugs, closely allied chemically, and having each a sharply defined predilection for muscle or for nerve. Veratrine acts upon muscle. Protoveratrine acts upon nerve. And the action of protoveratrine upon nerve is very similar to the action of veratrine upon muscle. Just as in muscle veratrine impedes the relaxation of a contracted state, so in nerve protoveratrine impedes the positive reaction that is normally associated with, or consequent upon, excited activity. Normal nerve gives during excitation a negative variation that signifies disintegrative change, and after excitation a positive return to, or it may be beyond, the normal level of a quiescent state, signifying reintegration. Veratrinised nerve acts and reacts normally. Protoveratrinised nerve exhibits a well-marked negative sign of action during excitation, but little or no positive sign of reaction after excitation. And in correspondence with this failure of positive reaction, the succession of action-effects exhibits rapidly progressing exhaustion. A succession of negative variations of normal (or of veratrinised) nerve, exhibits from first to last little or no diminution. Successive negative effects on protoveratrinised nerve are permanent and rapidly diminishing. Exhaustion is apparent in medullated nerve when its positive process of restitution is impeded.

III.—THE LAW OF REACTION.

The simplest problem that we may set ourselves to resolve in the case of any excitable tissue—such as muscle, nerve or retina—is to determine how much responsive effect follows upon how much exciting cause.

And we shall most conveniently summarise our results by plotting a curve, marking off magnitudes of cause (= excitation) along the X axis and magnitudes of effect

along the corresponding ordinates parallel with the Y axis.

Taking, for example, a series of stimuli of arithmetically increasing magnitudes, 1, 2, 3, 4, 5, and having determined that the corresponding effects come out at the magnitudes 34, 58, 72, 82, 90, the cause-effect curve plotted out on this principle would be thus :

FIG. 21.

Curve exhibiting the electrical response (Y) of the retina to luminous stimulation (X) of arithmetically increasing magnitude (energy). The unit of light in this case is $\frac{1}{10}$ th part of the light of a standard candle at a distance of 1 foot, *i.e.*, the light of a standard candle at a distance of 10 feet.

viz., concave to the abscissa OX, and exhibiting at a glance that + 24 + 14 + 10 + 8, diminishing increments of effect, are caused by equal increments of excitation.

Now let us plot out the results of an actual experiment in which the cause was luminous stimulation, and the effect an electrical response of the retina.

The X series was 1, 2, 4, 6, 8 units.

The Y series was 44, 60, 68, 72, 75 degrees of scale.

The plotted curve is obviously concave towards the abscissa OX, *i.e.*, equal increments of luminous excitation cause diminishing increments of retinal change.

FIG. 22.

Curve exhibiting the electrical response (Y) of the retina to electrical stimulation (X) of arithmetically increasing electrical energy (condenser discharges).

Let us take as another illustrative instance an experiment in which the cause was electrical stimulation and the effect a subsequent electrical response of the retina.

FIG. 23.

The X series was 20, 80, 180, 320 and 500 ergs.

The Y series was 4, 22, 34, 40 and 45 degrees of scale.

As before, the cause-effect curve is concave to the abscissa OX, *i.e.*, equal increments of cause produce diminishing increments of effect.

The cause-effect curve of stimulation and sensation, as expressed by the logarithmic law, is of a precisely similar type, *i.e.*, equal increments of sensation require increasing increments of stimulation, or otherwise expressed, diminishing increments of sensation are produced by equal increments of stimulation. Taking, *e.g.*, intensity of light along the X axis, and intensity of sensation along the Y axis, we require geometric increase of X to produce arithmetic increase of Y, or otherwise expressed, arithmetic increase of X produces logarithmic increase of Y.

This well-known and much criticised law of sensation, which with reservation may be admitted to be the fundamental law of psychophysics, holds good only within certain limits of moderate stimulation. Within the moderate range of ordinary daily sensation, it is obviously reasonable that equal increments of stimulation should effect decreasing increments of sensation, and that all sensation should find its limit with maximal alteration of nerve-matter. Between objective stimulus and subjective consciousness we have to consider physiological change of nerve-matter, of which change of consciousness is the symptom. An external stimulus *X* arouses physiological change of nerve-matter *Y*, which material change or internal stimulus *Y* is the basis of the sensation *Z*. Firstly, external stimulus, secondly, physiological change, thirdly, sensation—a relation between first and third such that equal increments of the former arouse decreasing increments of the latter. Is this limitation of effect, which is so clearly pictured in the concave curve, a limitation of physiological change *Y* producible by stimulation *X*, or a limitation of psychical change *Z* producible by physiological stimulation *Y*? Clearly, I think, the former—since we find in the case of the retina, or indeed in any case where the physiological effects of excitation are experimentally accessible, that equal increments of excitation arouse diminishing increments of physiological effect.

Less clearly, and with less confidence, yet, I think, with some degree of justification, we may assume, at least for the sake of clear thinking, the corollary to this conclusion, viz., that there is no disproportion between the physiological change *Y* and the psychical sensation *Z*, *i.e.*, that equal increments of sensation belong to equal increments of physiological change; or, again, that the symptom felt is the true arithmetic measure of the physiological state of nerve-matter which is its basis.

Let us consider rather more closely the two extremes of minimal and maximal sensation.

With indefinite increase of stimulation it is clear that we cannot have indefinite increase of physiological change, nor, therefore, indefinite increase of sensation. There must be a maximal effect. All change in living matter is, indeed, self-limitative; the activity of all living matter expends itself, and is arrested by the products of activity; with excessive stimulation the curve of sensation ceases to rise and then falls away from its maximum, losing itself finally in some other kind of sensation, or in actual anæsthesia through mere physiological exhaustion of nerve matter. Does such blunting of sensation come to pass through the agency of waste-products of excessive activity, of which carbonic acid is the representative? We may imagine so, but we may hardly say so.

At the lower end of the scale, down near the threshold of sensation, it is hardly reasonable to expect that a concave curve, constructed on the same formula as that, expressing the relation between moderate stimulation and moderate sensation, should express the relation between minimal stimulation and minimal sensation. Such a curve, steepest at its commencement, *i.e.*, with greatest increments of *Y* for given equal increments of *X*, would signify that close to the threshold absolute differences of *X* of infinitesimal magnitude take effect upon consciousness, *i.e.*, a condition of extraordinary hyperæsthesia towards the minutest stimuli of our environment.

We should expect to find, and in point of fact we do

find by careful experiment, that the minimum perceptible difference, *e.g.*, of light, is a considerably higher fraction at low intensity than at moderate intensity, *e.g.*, 1 in 5, or 1 in 10 at low intensity, as compared with 1 in 50 or 1 in 100 at moderate intensity. We all know indeed that it becomes more and more difficult to see print distinctly with fading light. This signifies that we are relatively less sensitive to differences of weak light, relatively more sensitive to differences of moderately strong light—in other words, that the early rise of the curve from the threshold is by increasing increments of sensation, *i.e.*, convex to the abscissa. A curve beginning thus, convex to the abscissa, and subsequently becoming concave to the abscissa, may be briefly designated as an S-shaped or sigmoid curve. To say that the cause-effect curve (cause measured along the X axis, effect along the Y axis) is a sigmoid curve, is to say in brief that equal increments of cause from minimal to maximal produce at first increasing increments of effect, and subsequently decreasing increments of effect. Fig. 24 is intended to make this point clear.

FIG. 24.

Curve exhibiting the electrical response (Y) of the retina to luminous stimulation (X) of low arithmetically increasing intensity (energy). The unit of light is here one quarter of the unit taken for Fig. 21, *i.e.*, the light of a standard candle at a distance of 20 feet.

I consider that a sigmoid curve as just defined gives graphic form, not merely to the relation between physical excitation and psychical sensation, but to the general relation between physical cause and physiological response in the excitation of living matter, of nervous matter, and in particular of the retinal substance excitable by light.

I look for, and find it, in the case of muscle, and in the case of nerve, and in the case of the retina, and venture to speak of it as the law of reaction.

A comparatively rough series of trials suffice to bring out data that are plotted in a curve concave to OX, *i.e.*, with diminishing increments of effect to equal increments of cause.

A more delicate series of trials, with stimuli of low intensity and increasing by smaller increments, is necessary to bring into evidence the initial convex portion which is comparatively short.

Fig. 25 is a good example of it upon the retina, strength of light being plotted along the X axis, magnitude of electrical response along the Y axis.

FIG. 25.

Let me try to illustrate the great general significance of a sigmoid curve, such as I have urged as symbolising more faithfully than the wholly logarithmic curve the law of physiological reaction, which I take to be inclusive of the law of psychical reaction.

The adequate performance of any human task is the effect of human energy—How much energy X to how much result Y in the asymptotic approach towards perfection?

In, let us say, the learning of a language, we know that the first steps cost much, and that the effect rises slowly; then the upward progress becomes more rapid, successive equal increments of energy give successive increasing increments of knowledge; finally progress slackens, the last steps towards perfection cost energy far in excess of those taken within the range of mediocrity.

The easiest part of any task, that in which the smallest effort seems to give greatest progress, is its middle portion; the two hardest and most expensive parts are its beginning and its end.

NOTES AND REFERENCES.

(1) INEXHAUSTIBILITY OF NERVE-FIBRE (p. 5).

I have insisted upon this point upon more than one occasion—for the first time in 1885 and in 1886 in two successive reports to the Scientific Grants Committee of the British Medical Association (*B. M. J.*, July, 1885, and July, 1886), for the second time in 1891 in a paper on the "Sense of Effort," communicated to the Neurological Society (*BRAIN*, 1891, pp. 179-433), and for the third time in the Croonian Lecture for 1896 (*Phil. Trans. R. S.*, 1897).

Wedensky in 1883 (*Cbt. f. d. Med. Wissenschaft*) and Bowditch (*J. of Physiology*, 1885; *Du Bois-Reymond's Archiv.*, 1890), came to the same conclusion, viz., that nerve-fibre is practically inexhaustible, and expressed themselves far more unreservedly than I then did, or should care to do now. The negative variation of nerve is an ultimate sign of life, and even if electrotonic effects are excluded, is not a safe proportional indicator of the capacity for function which requires not merely a living state,

but a living state of high excellence. A nerve that can conduct nerve-impulses will certainly manifest a negative variation, but it does not follow that a nerve that will manifest a negative variation is capable of conducting nerve-impulses.

I share the opinion expressed by Pflüger to the effect that the negative variation is itself proof positive of a chemical change in active nerve, that activity if long enough and strong enough *must* cause chemical expenditure, and, therefore, fatigue. But the anomaly of apparent inexhaustibility of nerve in the presence of undeniable chemical change, is in my view reconciled when we have recognised the extraordinary rapidity with which exchange of matter is effected between gray axis and white sheath. I regard the white sheath as forming a store of nutrient matter surrounding the gray axis—feeding it and fed by it—enabling the function to be performed, and itself a secondary deposit aroused by the function. In short, I regard medullated nerve as supplying a striking case of “complementary nutrition”—of that “consensus partium” between two mutually interdependent tissues according to which waste matter of each tissue is raw material to the other tissue.

(2) FATIGUE OF THE END-PLATE (p. 5).

In the illustration given in the text the effect on muscle has been produced by excitation of its nerve, and the decline is, therefore, by progressive fatigue of the end-plate.

This point was established in my reports to the Scientific Grants Committee of the British Medical Association for 1885 and 1886 (*B. M. J.*, July, 1885, and July, 1886), when I compared the state produced by fatigue and by nerve-degeneration with that produced by curarisation, and formulated the conclusion that the motor end-plate is the weak link in the neuro-muscular chain, being the point at which the function of transmission is first affected with excess of action, or with disordered nutrition or with the onset of death, just as in curarisation.

In voluntary action—involving changes throughout the tract from Rolandic cell to periphery—the chiefly fatiguable points are presumably the cells or points denuded of white matter, viz., the cerebral cell, the spinal cell, and the motor end-plate. I have elsewhere formulated the law that fatigue effects declare themselves with diminishing gravity from centre to periphery, *i.e.*, that central fatigue is limitative of peripheral fatigue.

(3) ISOLATED NERVE AS A TEST-OBJECT (p. 5).

The general application of the electrical method to the pharmacodynamics of isolated nerve was first broached and described in a series of three papers communicated to the Neurological Society in 1896, and published in *BRAIN*, 1896, pp. 43, 277, and 569.

The particular case of carbon dioxide is considered at length in the Croonian Lecture for 1896 (*Phil. Trans. R. S.*, 1897).

Other developments of the same subject are contained in the Proceedings of the Royal Society and of the Physiological Society for the years 1895 to 1899.

The fundamental principles of the method are given in my "Lectures on Animal Electricity," 1897.

(4) THE AXIOM OF GENERAL PHYSIOLOGY, p. 7.

The expression is of Claude Bernard (*Phénomènes de la Vie*, 1879, vol. ii.).

"On peut distinguer deux ordres de phénomènes :—

"(1) Les phénomènes de fonctionnement, ou encore d'usure, ou de *destruction vitale*.

"(2) Les phénomènes de formation, ou de création vitale, ou encore de *synthèse organique*. . . .

"Les deux types ne sont jamais isolés ; ils sont indissolublement connexes, et la vie de quelque être que ce soit est caractérisée précisément par leur réunion et leur enchaînement ; ils représentent les deux phases du travail vital.

"Cette vérité constitue, ainsi que nous l'avons dit ailleurs, *l'axiome de la physiologie générale*. On peut être assuré que toute doctrine qui serait directement ou indirectement en contradiction avec cette donnée fondamentale est fausse, et que le principe de l'erreur est précisément dans cette contradiction."

(5) POSITIVE AND NEGATIVE (pp. 8 & 9).

It is purely matter of convenience and convention which of two opposed movements we may choose to designate as positive and which as negative. But once having made our choice, the convention must be adhered to throughout the course of any given argument.

As regards muscle, the usual custom is to regard contraction as the positive act, relaxation as the negative act.

As regards the chemical changes, however, we are naturally led to take negative change (katabolism) as the chief feature of contraction, and to regard positive change (anabolism) as the reaction during relaxation.

As regards the electrical change, it is usual to refer to the poles of the external circuit, and not to the electro-motive elements. On this understanding the pole connected with active tissue is negative, just as the pole connected with the zinc of a voltaic couple is negative. In physiological literature active tissue is termed negative, whereas in physics the zinc carrying the negative pole is termed electro-positive.

I venture to think that the electro-motive action of active tissue is more vividly pictured when referred to an electro-positive element as the driving force, than when it is indicated by negative pole. Moreover, the latter custom introduces misleading expressions, such as "active tissue electro-negative to normal tissue," "negativity of action," &c.

Physiologically *active* tissue, in which presumably disintegrative exceeds reintegrative change, like the zinc of voltaic couple, is *electro-positive*, and its external pole is *negative*. Physiologically *quiescent* tissue, in which presumably reintegrative exceeds disintegrative change, is *electro-negative*, and its external pole is *positive*.

In any case, where there is danger of ambiguity from the terms positive and negative, direction of current should be clearly indicated by words or by diagram.

(6) RETINAL RESPONSE TO LIGHT (p. 9).

The variation of current of the illuminated eye was discovered by Holmgren in 1871 (*Cbt. f. d. med. Wiss.*, 1871, p. 423), and further investigated in 1873 by Dewar and McKendrick (*Trans. R. S. Edin.*, 1873, p. 141; *Journ. of Anat. and Physiology*, vii., p. 275, 1873), and in 1880-81 by Kühne and Steiner (*Unters. a. d. physiol. Inst.*, Heidelberg, vols. iii. and iv., 1880-81).

Holmgren described the retinal response to light as being positive in the case of the frog, negative in the case of mammals.

Dewar and McKendrick sum up their observations on the frog's eye as follows:—"The natural electro-motive force is in the first place increased, then diminished; during the continuance of light it is still slowly diminished to a point where it remains tolerably constant; and on the removal of light there is

a sudden increase of the electro-motive power nearly up to its original position."

Kühne and Steiner in their second paper (*Sehorgan*, 1881) give an account of retinal phenomena in many respects similar to that which I have given in the text, of the successive changes as they came under my observation. K. and S. insist particularly upon the permanently positive response of the normal eyeball and upon its alterations by injury. They consider the negative effect to be produced by partial detachment of the retina, and the positive effect during illumination to be the expression of a regenerative influence of the retinal epithelium.

These and other points will be more fully discussed in a paper that I am now drawing up for communication to the Royal Society.

Quite recently (November, 1899), Beck has described the retinal response of the cephalopod retina as positive (*Pflüger's Archiv.*, vol. lxxviii., p. 129, 1899).

(7) LATENCY OF THE RETINAL RESPONSE (p. 12).

Dewar and McKendrick made the first approximate measurements of latency, and found it to be not more than $\frac{1}{10}$ th sec.

S. Fuchs (*Pflüger's Archiv.*, vol. lvi., p. 408, 1894), with the aid of Bernstein's rheotome, measured it as being 0.0004 to 0.006 sec.

(8) TETANISATION OF THE RETINA (p. 8).

I have since made the experiment alluded to in the text. The results are altogether similar to those obtained by illumination. Alterations of retinal excitability are manifested in a nearly parallel sense to both kinds of stimulation. During and after tetanisation the retinal excitability to light is increased. The results of these experiments will be published shortly.

(9) HERING'S THEORY OF COLOUR VISION (p. 18).

Hering first promulgated his celebrated theory in the sixth of a series of communications to the Vienna Academy of Sciences in the years 1872 to 1874, collected and reprinted for the second time in 1878 under the title *Zur Lehre vom Lichtsinne*.

The paraphrases of Hering's theory current in English textbooks are far less subtle and indefinite than the version of

Hering himself, who writes as follows in the introduction of a paper by Hillebrand (*Wiener Sitzungsberichte*, February, 1889, p. 73):—

“The psycho-physical vision-stuff may accordingly be regarded as a mixture of three qualitatively different substances. Nevertheless, I signified long ago (*Zur Lehre vom Lichtsinne*, § 42) that I gave this form to the theory only for the sake of greater distinctness, and that I consider it to be fundamentally more correct to say that the psycho-physical vision-stuff is capable of qualitatively different kinds of Dissimilation and Assimilation, and that each of these innumerable different kinds of D. and A., assuming three principal kinds of D. and A., can be conceived as broken up into three components, each of which corresponds to one of these three principal kinds of D. and A. It is, no doubt, more intelligible to most people to say that each visual sensation may be conceived as composed of given primary or elementary sensations, in given proportions, than to say that each visual sensation takes, in the pre-arranged three-dimensional variability of visual sensation, a given place in relation to three given sensation series; and it is more intelligible to regard the vision-stuff as a mixture of three separate substances, each of which can be altered in two qualitatively opposite senses ($D. > A.$ and $A. > D.$), than to say that the variability of state of vision-stuff is three-dimensional.”

Helmholtz's theory, with which Hering's is generally quoted as being in flagrant opposition, is hardly more accurately reproduced in English text-books. In the second edition of his “*Physiological Optics*” (1889, p. 349), he assumes the hypothetical existence not merely of three sorts of retinal elements, but of three kinds of photo-chemically changeable substances, and of three kinds of cells in the cerebral cortex.

On a hypothesis of antagonistic colours of so meta-chemical a character as Hering's, positive results of experiments of the character described in the text might hardly be expected.

Previous experiments of the kind have been published by Dewar and McKendrick, who observed a different order of efficacy to that given in the text, viz:—red = 10, yellow = 10, green = 8, and blue = 4. Subsequently, however, they give the relative efficacy of colours as being governed by luminosity.

R. Dubois (*La Pholade Dactyle*, Paris, 1892) tested the efficacy of different colours upon the mechanical response of the integuments of *Pholas dactylus* with the following result:—red = 3, yellow = 13, green = 10, blue = 8. These numbers represent amplitude of reflex contraction of an integument excited by

spectral colours. With coloured glasses the results were:—red = 3, yellow = 13, green = 10, blue = 8. With the same set of glasses—which Professor Dubois was good enough to send to me—I obtain electro-motive responses of the frog's retina as quoted in the text, viz.:—red = 4, yellow = 16, green = 12, blue = 8.

The researches of Dubois on the integument of *Pholas* are of great interest as regards the general physiology of luminous excitation, but are not yet sufficiently appreciated. There is a close structural and functional analogy between the retina and the integument of *Pholas*. Both respond to light—the former by an act of vision and by an electro-motive change, the latter by a reflex mechanical movement and an electro-motive change. The physiological histology of the sensitive surface is as follows:—An external layer of pigment-cells is connected with a superficial layer of muscular fibres that contract in response to luminous stimuli; this initial direct contraction mechanically stimulates subjacent nerve-cells, and is followed, after a short interval of time, by a reflex contraction of the entire longitudinal musculature of the syphon. Histologically, the dermic element excitable by light is composed of (1) a pigment-cell, (2) a contractile fibre, and (3) a nerve-cell. Physiologically, the stimulus of light arouses a dermic phosphene, of the nature of a tactile phenomenon, *i.e.*, light provokes chemical change in a pigment-cell, which in turn provokes movement of a contractile fibre, which in its turn mechanically excites a nerve-cell. This series of events at the periphery constitutes the physiological stimulus of which a reflex contraction of the syphon is the final consequence, just as a reflex movement of self-defence or flight is the final consequence of the retinal changes aroused by retinal images higher in the animal scale.

(10) HERING'S POSITIVE AFTER-EFFECT (p. 20).

A full description was first given of the after-effect of nerve-excitation and of its possible significance by Hering in 1884 (*Wiener Sitzungsberichte*, 1884, p. 137). The point was further investigated in Hering's laboratory by Head (*Pflüger's Archiv.*, vol. xl., p. 207, 1887).

(11) THREE STAGES OF NERVE-RESPONSE (p. 20).

The three stages into which I found it necessary to distinguish the response of isolated nerve, and the possible signifi-

cance of the phenomena observed in each stage, are fully discussed in the Croonian Lecture for 1896 (*Phil. Trans. R.S.*, 1897, pp. 23 and 62).

(12) RAPIDITY OF NERVE-POLARISATION (p. 20).

Hermann pointed out in 1888 (*Pflüger's Archiv.*, vol. xlii., p. 1, 1888) that nerve, unlike muscle, exhibits no difference of resistance, whether the test-current be a constant or an induced current. Nerve is eminently polarisable (Herman's well-known theory of electrotonus rests upon this basis), but its polarisation and depolarisation take place with such extreme rapidity that the polarisation counter-current has time to develop even during the passage of an induction current.

Following up this point I found that the apparent resistance of normal nerve is higher to the comparatively "long" induced current at make than to the comparatively "short" induced current at break. Also that the apparent resistance of nerve to any current is diminished by diminution of polarisation counter-current, when the nerve-matter has been "immobilised" by chloroform (*Proc. Physiol. Soc.*, November, 1898).

(13) VERATRINE AND PROTOVERATRINE (p. 21).

The action of *veratrine* upon muscle was first described in 1862 by Harless (*Ztschr. f. rat. Med.*, iv., p. 97, 1862), and further studied by v. Bezold and Hirt (*Unters. a. d. physiol. Lab.*, Würzburg, 1867), J. L. Prevost (*Gazette médicale de Paris*, 1867), Fick and Boehm (*Arch. a. d. physiol. Lab.*, Würzburg, 1873), and many others.

Protoveratrine was identified and separated in 1890 by Salzberger, and its properties investigated by Watts Eden in the Pharmacological Institute of Leipsig, under the direction of Professor Boehm. W. Eden observed that protoveratrine, although poisonous to muscle, does not cause the prolongation of contraction characteristic of veratrine. The protoveratrine with which I made the experiments alluded to in the text, was kindly given to me for the purpose by Professor Boehm. I have described the results somewhat more fully in the jubilee volume of the *Société de Biologie*, Paris, 1899, p. 347.