**The peculiarities of sensibility founds [i.e. found] in cutaneous areas supplied by regenerating nerves / Wilfred Trotter and H. Morriston Davies.**

# JOURNAL

FÜR

# PSYCHOLOGIE UND NEUROLOGIE

HERAUSGEGEBEN VON

AUGUST FOREL UND OSKAR VOGT

REDIGIERT VON

K. BRODMANN

SONDER-ABDRUCK



LEIPZIG 1913
Dörrienstr. 16
VERLAG VON JOHANN AMBROSIUS BARTH

**Verlag von Johann Ambrosius Barth in Leipzig.**

Das aus der Zeitschrift für Hypnotismus und Psychotherapie hervorgegangene

# Journal für Psychologie und Neurologie

herausgegeben von

**August Forel** und **Oskar Vogt**

redigiert von

**K. Brodmann.**

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2. speziell ärztlich-psychologischer Natur sind und zwar
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*Sonder-Abdruck aus*
*„Journal für Psychologie und Neurologie“*
*Band 20, 1913.*
*Verlag von Johann Ambrosius Barth in Leipzig.*

**WILFRED TROTTER (University College Hospital, London) and H. MORRISTON DAVIES (University College Hospital, London).** **The peculiarities of sensibility found in cutaneous areas supplied by regenerating nerves.**

(From the Research Laboratories of University College Hospital Medical School, London.)

With 6 Figures.

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### Introduction.

The processes whereby a peripheral nerve which has been divided regains its normal activity are of great interest to the physiologist as well as to the clinician and have been extensively studied by both. In so far as motor nerves are concerned the physiologist has been able to deal with the subject in both its principal aspects namely the histological phenomena of the anatomical restoration of the nerves and the phenomena of the recovery of function. In a general way the results thus obtained agree with those observed by the clinician in the human subject, allowance being made for the fact that in the latter case the recovery is from lesions made accidentally and not under experimental conditions.

In regard to sensory nerves however the case is different. Here the investigations of the physiologist are almost necessarily limited to histological observations and he has not been able to make by animal experiments exact enquiry into the recovery of function.

It was for a long time assumed that the recovery of sensory function was a gradual and uneventful restoration to the normal corresponding with the histological events of regeneration, possibly varying in length in different cases but tending always in time to be complete. The area of skin deprived of sensibility by the nerve section would thus shew during recovery no form of sensibility which

could not be described as a hypoaesthesia. It would be stating the case very moderaelty to say that such an orderly progress of events was unfamiliar to the clinician. Many unaccountable peculiarities of sensibility were from time to time observed to occur but as they were not explained or even described by the physiologist and were phenomena particularly insusceptible to exact description by the clinician they tended to be regarded as in some way accidental and not essential accompaniments of the functioning of the sensory nerve during recovery.

In 1905 an important contribution to the subject was published by *Henry Head*. He had made the great step in advance of applying the methods of experimental physiology to the investigation of the problem in the human subject and had submitted to the production of an area of anaesthesia in his own forearm and hand by the section of the cutaneous nerves supplying it. The nerves had been sutured and the ensuing phenomena closely observed and these phenomena studied for the first time under experimental conditions were found to be capable of exact and detailed description. Many of them were of a remarkable and unexpected character and the whole body of observations was used as the foundation for a hypothesis concerning the intimate physiology of the peripheral nervous system even more striking than the facts upon which it was based.

Both the facts and the hypothesis of *Head* were striking enough to make it clear their full value could scarcely be appreciated until they had been confirmed by investigations in which the same method was used by other observers and it was with this object in view that in 1907 we began a series of experimental nerve sections upon our own cutaneous nerves. In this investigation our guiding principle was that nerves should be cut in both of us at different times so that the material on which our conclusions were to be based should be drawn from as wide a field as possible and also so that the knowledge gained in investigating the phenomena of one experiment could be used to amplify and coordinate our methods in the next.

In this communication we propose first to describe and examine the facts of the recovery of function after section of a sensory nerve comparing our observations with those of *Head* and attempting to indicate those which we regard as definitely established. Secondly to discuss the various hypotheses which have been advanced in explanation of any or all of these facts. And thirdly to put forward certain views of our own which our investigations have led us to entertain.

## Phenomena of Recovery.

### a) *Material on which observations are founded.*

It will be convenient to begin with a summary account of our own personal observations. The material for these was obtained by the division in one or the other of us of the following nerves: Internal saphenous, Great auricular, Internal cutaneous of arm (nervus cutaneus brachii medialis), a branch of the middle cutaneous of thigh.[1]) In the case of the internal cutaneous the whole area of distribution of the nerve was rendered anaesthetic by dividing its three branches at three separate operations. In order that the basis of enquiry might be as broad as possible we

[1]) In every case a piece of the nerve trunk from 5 to 10 mm in length was excised and the ends united by sutures.

chose nerves in widely different parts of the body and of very different sizes varying from such as supplied small areas, to nerves like the internal saphenous and the internal cutaneous, the section of which produced areas of anaesthesia of 280 sq. c. m. and 122 sq. c. m. respectively. To obtain material for very exact comparison of results in two different individuals, a branch of the middle cutaneous of the thigh in each of us was divided. These precautions made the research very prolonged but justified themselves in the extent and diversity of the experience they gave us.

To such as may be disposed to prosecute researches in this department of physiology we would take this opportunity of remarking that proportionally to the interest of the work the amount of inconvenience incident upon having a cutaneous nerve or two divided is extremely small. It would be easy for anyone without actual experience to overestimate the discomforts of these small essays in experimental physiology. The largest nerve we cut was the internal saphenous at the knee and the section rendered anaesthetic nearly the whole of the inner aspect of the leg. Yet the subject of the operation has experienced from the lesion nothing but the most inconsiderable discomfort at any time. It is true for reasons we shall have to refer to in the concluding section of this paper, that a certain degree of temperamental stability is desirable in the subject of such an interference but this is of course also necessary for the general work of the observations if results capable of reliance are to be obtained.

### b) *First Appearances of Recovery.*

We do not propose to enter upon the description of the alterations of sensibility produced by the nerve section: this has been dealt with fully in our earlier paper.[1]) It may however be stated that each area of sensory defect shewed for some weeks previous to the first appearance of recovery a well defined, stable and stationary condition. In the central part of the area there was profound loss of cutaneous sensibility of all kinds and surrounding this was a fringe of varying width which shewed a hypoaesthesia to all forms of stimulation; this hypoaesthesia being most intense towards the central part of the area and diminishing gradually away from it. We wish to lay particular stress upon the fact that in this quiet period immediately preceding the first appearance of recovery we never observed any phenomena except those of reduced sensibility and it frequently happened that the possessor of such an area of sensory loss was quite unconscious of its presence in the intervals between examinations. As soon however as recovery began the subject became more or less continually aware of the abnormal region of his skin.

The first clear evidences of the beginning of the restoration of function were usually to be observed between the 10$^{th}$ and 12$^{th}$ weeks after the nerve section. Thermal sensibility, tactile sensibility and sensibility to pain began to reappear in all cases about the same time; and it is interesting to notice that the motor functions of the cutaneous nerves (pilomotor, sudomotor) shewed signs of beginning restoration at about the same period. In every case the reappearance of function occurred first in the proximal part of the affected area at and about the spot where the nerve entered it. Beginning thus the evidences of recovery spread gradually

1) "Experimental Studies in the Innervation of the Skin". Journal of Physiology. Vol. 38 Nos. 2 and 3. 1909.

towards the distal extremity of the area. The time taken for complete restoration to the normal was at least many months and usually more than a year. In regard to this matter however it is very important that a clear distinction should be made between restoration of sensory acuity and restoration of the normal quality of sensation. The former, when it occurs is always much more rapidly completed than the latter, and it is to the former that the periods specified above refer.

Sensibility to all forms of stimuli is, as is well known, distributed in the skin in minute areas or spots and when a region is recovering sensibility as a result of regeneration of its nerve the reappearing function is localised in isolated spots also.

It would seem to be very generally taken for granted that when the ends of a nerve have been stitched together, and the wound has healed without suppuration, complete recovery of function is merely a question of time. The process of recovery may in fact however be arrested at any stage and a permanent defect of sensibility remain.

### c) *Return of Sensibility to Touch.*

The sensation elicited by tactile stimuli is to the trained observer one of the most definite and characteristic which he can experience. It possesses qualities which mark it off from all other sensations as clearly as is marked off the sensation of cold or that of pain. *von Frey* has shewn that the peripheral mechanism of this form of sensibility is intimately associated with the hair bulbs, that the movement of the hair bulb is essential to the production of the sensation and that therefore the stimulus which calls forth the sensation must be an actual movement at the moment the sensation is produced. In other words when the skin is touched a tactile stimulus is given at the moment when contact is made and at the moment when contact is broken but not in the interval if the stimulating object is kept in motionless contact with the skin. The best method of investigating this form of sensibility is the well known hair aesthesiometer of *von Frey* which enables exact quantitative estimations to be made. Examination of an area in the quiet period before the appearance of recovery will shew a central region in which the characteristic tactile sensation cannot be elicited with any of the *von Frey* hairs, however strong; surrounding this and between it and the normally sensible skin is a relatively narrow zone in which the sensation of touch can be elicited but only with hairs stronger than those necessary to stimulate normal touch spots.

It will be found about 10 to 14 weeks after the nerve section that this hypoaesthetic zone begins to increase at the expense of the anaesthetic area in the region where the nerve trunk enters it. That is to say a few spots will be found in this region, where at former examinations no touch sensation could be elicited, which now yield that sensation but only when stimulated by hairs giving a stimulus well above the normal threshold of the part. It is clear therefore that although sensibility to touch returns thus early, it reappears in a distinctly hypoaesthetic form so that the return of it at this date might very easily be altogether overlooked if the examination for it were made by a method which involved the use of a stimulus of fixed strength such as that given by cotton wool or a camel's hair brush.

During the ensuing months the return of sensibility to touch gradually extends throughout the area from the proximal to the peripheral extremity, always

appearing first along the line of the nerve. By the 6th to the 8th month, supposing recovery to be proceeding in the normal way, touch spots, from which the characteristic sensation can be elicited will have appeared throughout the whole area though not distributed with their normal density. Most of the spots however will still be distinctly hypoaesthetic and will need a stimulus well above the normal threshold to yield tactile sensation. It is not therefore until after this period that the area begins to respond to stimulation with cotton wool. The sensibility thus regained shews certain other peculiarities than hypoaesthesia. These peculiarities concern the quality of sensation and the localisation of it. First as to quality, it may be said that while each touch felt has the characteristics of that sensation, it possesses also certain other features which the subject recognises as being altogether new but very difficult to define. The sensation has a certain sharpness in it, not recognisable in a normal touch and resembling somewhat the tingling vibration produced by the faradic current. This peculiarity is not very easily detected during the stimulation of a single touch spot with a *von Frey* hair but is very striking when a considerable area of recovering skin is stimulated at one time. With regard to localisation a very striking phenomenon is noticeable from the first moment of recovery and this is that when a recovering spot, necessarily of course at the proximal end of the area is stimulated, the corresponding sensation, instead of or in addition to being felt locally, is felt in the extreme peripheral end of the area which is still at this early stage anaesthetic: this is the phenomenon which we have called "peripheral reference". As we shall see later it is not peculiar to tactile sensations. It is one of the earliest and most characteristic accompaniments of recovery and also one of the most persistent for it may be quite definitely observable years after the area has recovered its normal sensory acuity.

### d) *Return of Thermal Sensibility.*

In the period preceding the first appearance of recovery, the affected area presents a central region of thermo-anaesthesia surrounded by a zone of thermo-hypoaesthesia which gradually fades into the normal sensibility of the unaffected skin.

The study of thermal sensibility is a peculiarly difficult one not only in regard to technical detail but especially in regard to obtaining clear conceptions on the subject and expounding them without confusion. It is particularly important that a perfectly definite idea should be obtained as to what is meant by thermo-hypoaesthesia. Thermal sensibility is localised to two series of spots scattered in the skin, one series being sensitive to temperatures above, and the other sensitive to temperatures below that of the skin at the moment of testing. It seems that the peripheral mechanism whereby a thermal sensation is aroused depends upon the transference of heat to the skin or the abstraction of heat from the skin by the stimulating object, the former type of interchange always stimulating one series of thermal spots (heat spots), the latter type of interchange stimulating the other series (cold spots). When it is kept in mind that thermal sensibility registers heat transference and in no sense absolute temperature, it becomes clear that the temperature of the skin itself is of fundamental importance in determining whether stimulation by an object at a temperature at all near that of the skin will produce

a sensation of the cold series, a sensation of the heat series or no thermal sensation at all. It is common knowledge that an object may be made to feel cool or warm according to the temperature of the skin without its own temperature being altered, but it is not equally obvious that objects whose temperatures are very near that of the skin can give rise to no thermal sensation at all. There is however in fact an insensibility of the skin to temperatures ranging over about 5 degrees centigrade of the thermo-metric scale. This normal intermediate insensibility can of course be shifted upwards or downwards by warming or cooling the skin respectively. Thermal stimuli bordering on this range of intermediate temperatures give rise to sensations of very slight intensity, cool or warm in quality according as the stimulus is below or above the temperature of the skin. As the stimulus temperature departs from that of the skin, so the corresponding sensation becomes more intense, and it is generally necessary for there to be a difference of 15 degrees between the stimulating object and the skin before the maximal sensation — cold or hot — is elicited. If we now consider what would be the effect of a general reduction in the thermal sensibility of the skin it becomes obvious that this must produce an increase in the range of intermediate insensibility and a diminution in the intensity of sensations produced by the various stimulus temperatures. For example suppose on normal skin an object at 32° C to be indifferent, one of 35° C faintly warm, one of 38° C warm and one of 50° C hot. If such an area of skin becomes hypoaesthetic 32° C and 35° C will now both be indifferent, 38° C will be faintly warm and 50° C will be warm while it may not be possible to elicit the sensation "hot" by any temperature. This is the condition which we found to obtain after nerve section in the zone of thermo-hypoaesthesia surrounding the area of thermo-anaesthesia. The first sign of recovery occurs about the same time and in the same region as the reappearance of sensibility to touch. It consists in the development of a few spots in the most proximal parts of the affected area which yield sensations of cold when stimulated with a cold object. The nature of the sensibility of these spots is however peculiar in that the sensations elicited by stimulation are very intense and the phenomenon of peripheral reference is very clear. It would be impossible to exaggerate the intensity of the sensation of cold yielded by these spots whether it is felt locally or at the place of peripheral reference. As is well known the intensity of the sensation of cold produced by stimulation of normal skin varies directly with the size of the area stimulated. In order therefore to get some actual measure of the intensification of sensation in these recovering cold spots it is necessary to find by experiment how large an area of the normal skin must be stimulated to produce a sensation of equal intensity. We found that a single active cold spot in a recovering area stimulated with a metal cylinder having a contact surface 1 mm in diameter gave a sensation as intense as that produced by stimulation of normal skin with a metal disc at the same temperature as the cylinder but 25 mm in diameter, that is to say the sensation yielded by this cold spot was equivalent in bulk to that yielded by an area of normal skin 600 times as large.

Recovery progresses by the gradual spread throughout the area of reappearing cold spots accompanied by the characteristic intensification and peripheral reference. These latter phenomena are found not merely in the area previously anaesthetic but also in the zone previously hypoaesthetic.

The reappearance of sensibility to temperatures above that of the skin is a slower process and usually lags behind that of sensibility to temperatures below that of the skin by some months. The restoration of sensibility to heat however when it does begin, occurs and proceeds in the same way, namely by isolated and slowly thickening groups of spots. In addition to the restoration of sensibility to heat being actually a slower process the delay is rendered more evident by the facts that the heat spots appear in smaller numbers and are consequently more difficult to find than the cold spots and that all testing for sensibility to temperatures above that of the skin is especially difficult.

Another mechanism contributing to this delay is probably the following. As we shall shew all other sensations during recovery display a marked and characteristic intensification. Now the fully developed normal sensation "hot" is not without a certain element of sting easily accessible to introspection. This sensation under normal circumstances is elicited by temperatures of about 50° C. With temperatures but little higher the thermal element in the sensation rapidly diminishes and the pain element rapidly increases until at about 55° C or even less we get a sensation of stinging pain which although we may suspect it from its character to be of thermal origin yet has little or no true thermal quality. If then sensibility to heat has during recovery that intensification which all other sensations shew — and there is strong reason to believe that this is the case — stimulation of the returning heat spots with temperatures which normally elicit the sensation "hot" will yield sensations of stinging pain having little or no true thermal quality. This is found in fact to be the case. At a comparatively early period of recovery while the general surface is not particularly sensitive to temperatures about 50° C, certain spots will be found where this stimulus produces a stinging pain. It would seem then that these spots are in reality heat spots, their true quality being masked by the phenomenon of intensification. As recovery progresses and the sensation "hot" is beginning to be felt locally the peripherally referred sensation which accompanies it may still be one of stinging pain only.[1])

The three outstanding peculiarities of returning thermal sensibility are the delay in the restoration of sensibility to heat and the intensification and peripheral reference of the sensation of cold elicited from the cold spots. When cold spots first reappear they tend in spite of the intense sensations they are capable of giving rise to, to shew a certain hypoaesthesia; that is to say they may be of less than normal activity in regard to discrimination and to the recognition of temperature but little below that of the skin. The intensification and the peripheral reference then, are phenomena superadded to the series of changes constituting recovery rather than interposed among them as a necessary stage. It thus happens that they persist long after recovery is otherwise complete. Then very gradually the intensity of the cold sensations diminishes though peripheral reference of them may last still longer. In one of the areas which we investigated 5 years after the nerve section and at a time when the most delicate examination revealed no defect of sensory acuity whatever, there was distinct peripheral reference of sensations

[1]) This statement applies to stimulation made with test cylinders 1 mm in diameter. When a stimulating object of large surface is used peripheral reference of heat is distinct.

of cold and although these sensations had lost their former startling intensity they were very distinct.

e) *Return of Sensibility to Pain.*

The return of sensibility to pain shews all the phenomena of recovery, namely hypoaesthesia, intensification and peripheral reference. In order to make quite clear the results of our observations a few preliminary considerations must be dealt with.

The investigation of sensibility to pain is sometimes made by using the prick of a needle as a stimulus. As we have already pointed out in dealing with tactile sensibility a stimulus capable of minute graduation is essential in the detailed investigation of any sensory change and it is this fact which renders the use of the needle quite unsuitable for fine work. Various algometers have been invented from time to time but none of them have been found wholly satisfactory. Those making use of a pin prick as stimulus are undoubtedly the least unsatisfactory; but the method of graduating the pressure applied is in most forms complicated and in some unreliable. No method of graduating small pressures more satisfactory than the *von Frey* hairs has come to our knowledge, and we found that by applying it to graduate the force of pin pricks a simple and practical algometer could be made.

In the quiet period immediately preceding the first evidences of recovery sensibility to pain shews a central area of complete loss surrounded by a zone of partial loss. If this hypoalgesic zone be tested with the hair algometer it is found that the nearer a given spot is to the central analgesia the stronger is the pressure upon the needle necessary to elicit the sensation of pain, and conversely the farther from the central area the spot stimulated, the nearer is the stimulus pressure to that which elicits pain when applied to the normal skin. The sensations produced in this hypoalgesic zone are qualitatively perfectly normal. There is about them no abnormal unpleasantness whatever and their sole difference from sensations elicited by stimulation of the normal skin is that they need a stronger stimulus to call them forth. This absence of any abnormal quality makes very striking the first appearance of recovery because the quality of returning sensibility to pain is markedly abnormal, The first appearances of restoration begin about the same time as do those of sensibility to touch. In the most proximal part of the affected area pin pricks now call forth sensations of pain which are abnormally unpleasant and are referred to the peripheral part of the area. The unpleasant quality of these pain sensations is very distinct; it causes the subject of them to feel a scarcely controllable impulse to move the part and a strong inclination to rub, not the place where the stimulus has been given, but the place to which the sensation was referred. It is a remarkable fact that this rubbing of the seat of peripheral reference, although the latter may be a foot or more away from the spot to which the stimulus was applied does give considerable relief. It is thus clear that there is some relation between the phenomena of intensification and peripheral reference. At first at any given spot this returning sensibility to pain is distinctly hypoaesthetic, that is to say although the stimulus pressure used now yields a sensation where previously it yielded none yet such pressure has to be stronger than that necessary to call forth a sensation when applied to normal skin. In process of time sensibility to pain spreads throughout the affected

area retaining however its abnormal qualities but gradually becoming less and less hypoalgesic. There is no observable relation between hypoalgesia and abnormal quality; in fact the latter persists for months or even years after normal sensory acuity has been obtained.

f) *Summary.*

We are now in a position to state summarily the characteristics of sensibility accompanying restoration of function due to the regeneration of a nerve. These may be stated in the following propositions:

1. All forms of sensibility tend to reappear together, except sensibility to temperatures above that of the skin which is somewhat delayed; this delay is probably in part, at any rate, due to the difficulty of demonstrating sensibility to heat in its hypoaesthetic form, and to the effects of intensification.

2. All returning sensibility is at first hypoaesthetic.

3. All returning sensibility shews the phenomena of Intensification and Peripheral Reference.

4. Intensification and Peripheral Reference bear no relation to hypoaesthesia and persist long after restoration of sensory acuity is complete.

**Observations of Head and his collaborators.**

The observations of Head upon the special physiology of the peripheral nerves and the conclusions he draws from them are embodied in a series of bulky and elaborate contributions, some of which are wholly devoted to the subject while others contain more or less detailed reference to it. The list of papers is as follows.

The Afferent Nervous System from a New Aspect. Head, Rivers and Sherren. Brain, Nov. 1905.

The Consequences of Injury to the Peripheral Nerves in Man. Head and Sherren. Brain, Nov. 1905.

The Grouping of Afferent Impulses within the Spinal Cord. Head and Thompson. Brain, March 1907.

A Human Experiment in Nerve Division. Rivers and Head. Brain, Nov. 1908.

Sensory Disturbances from Cerebral Lesions. Head and Holmes. Brain, Nov. 1911.

Two only of these are entirely concerned with the results of the production in Head himself of an area of sensory defect by experimental nerve section. The first of these contains a general exposition of the interesting hypothesis which this experiment had led him to form, while the second comprises a detailed statement of the investigation and a discussion of various matters rising out of it.

The other three articles do not directly concern us here as the facts of observation they contain are derived from the clinical investigation of patients and are therefore by common consent of inconsiderable value as physiological data. In so far however as they do deal with matters of general principle we shall have to refer to various passages in them.[1])

[1]) In referring to the observations and conclusions recorded in these various contributions we shall for convenience use the name of Head only, without discriminating in each instance with which of his collaborators the particular work in question was done.

a) *Tactile Sensibility.*

One of the most striking of Head's observations was that recovery of sensibility to tactile stimuli began very much later than recovery of sensibility to thermal and painful stimuli.

"*Forty three days* after the operation the extent of the cutaneous analgesia had begun to diminish."

"*One hundred and sixty one days* after the operation cotton wool began to produce a diffuse tingling sensation over the forearm when the hairs were stimulated, but the whole of the affected area still remained insensitive to *von Frey's* tactile hairs."

"*Two hundred and twenty five days* after the operation the hairs on the back of the hand responded with diffuse tingling to cotton wool but the whole affected area of the forearm and hand still remained insensitive to *von Frey's* tactile hairs. This sensibility to cotton wool disappeared at once if the arm was carefully shaved."

"*Three hundred and sixty five days* after the operation the proximal patch on the forearm began to be sensitive to cotton wool after shaving." A Human Experiment etc. p. 341.)

It is clear however that stimulation of hairs had yielded sensations a great deal earlier than the period mentioned above as is shewn by the following quotation.

"The hairs within the affected area of the forearm and hand remained totally intensitive to all forms of stimulation until 86 days after the operation. We then discovered that within the upper patch on the forearm lay four hairs from which a sensation was evoked by pulling. At a distinct interval after the hair was pulled *Head* experienced a slowly developing vague sensation which was neither definitely painful nor unpleasant. It died away and recurred as a painful sensation which faded and again recurred as pain. The sensibility of these four hairs varied greatly; but slow development and a tendency to recur were the most certain characteristics of the sensation evoked when they were stimulated. This mode of reaction of the hairs was the beginning of the gradual restitution of a certain form of sensibility" (ibid. p. 385). It would seem then that the facts observed by *Head* were that sensations could be elicited by powerful stimulation of the hairs (pulling) at an early period of recovery (86 days); that the hairs become more and more sensitive to stimulation until at 161 days the comparatively weak stimulus of cotton wool elicited sensations; but that it was not until much later that cotton wool applied to the skin itself was felt.

He observed certain peculiarities of the sensations yielded by stimulation of the hairs. For example he says, speaking of the period 254 days the operation" . . . no part of the affected area which possessed hairs failed to respond.

This response was of the same extraordinary character as that with which we became familiar when testing the hairs of the forearm and consisted of a general tingling. Not only was it diffused widely but a sensation was evoked which seemed to lie over parts of the affected area remote from the point of stimulation" (ibid. p. 386).

From the facts that an area in the condition described in the last quotation is, when hairy, sensitive to cotton wool but insensitive to the same stimulus when shaved, while normal skin remains sensitive to cotton wool after shaving; and from

the fact that the sensations elicited by stimulation of the hairs in such an abnormal area are of distinctly abnormal quality, *Head* draws the conclusion that the hairs in the recovering area at this period "had become endowed with a form of sensibility independent of that usually called light cutaneous touch" (ibid. p. 387).

As we shall see later he associates this hypothetically distinct "hair sensibility" with what he calls the "protopathic" system of nerve fibres, which he regards as distinct from the system — "epicritic" — which subserves ordinary tactile sensibility. The process of recovery of sensibility to light touches is therefore according to *Head* somewhat complex; a peculiar form of sensibility to light touches returns first to the hairs and then after a long interval, sensibility to light touches returns to the skin itself.

When *Head's* observations on this subject and our own are compared the outstanding feature is the direct conflict of fact as to the time when tactile sensibility first reappears. According to us it returns about the same time as other forms of sensibility and often as the first manifestation of recovery, whereas according to *Head* it is very late and did not reappear in his own case for 12 months. Fortunately a good deal of light is thrown on this discrepancy by *Head's* own observations on hair sensibility.

In giving our own results we have insisted that tactile sensibility, like all other forms of sensibility, returns at first in a hypoaesthetic form; that is to say there will be a period during recovery in which the sensations characteristic of light touch can be elicited but only with a stimulus adequate for a threshold higher than that of the normal skin. With the use of such stronger stimuli (the heavier *von Frey* hairs) we have demonstrated repeatedly the reappearance of tactile sensibility between 80 and 90 days after the operation, just at the period that is to say when *Head* found that mechanical stimulation of the hairs gave rise to sensations and at a period of course when stimuli about the normal threshold, e. g. cotton wool, were not felt. It is of some interest that while *Head* insists repeatedly upon the fact that sensibility to pain and sensibility to thermal stimuli return at first in a hypoaesthetic form, that is with a high threshold, he did not, as far as we are aware make any thorough investigation of the possibility that tactile sensibility might also be returning in a hypoaesthetic form. His investigations of tactile sensibility seem to have been carried out chiefly with the use of cotton wool as a stimulus and to some extent with the lighter *von Frey* hairs. In regard to the use of the latter we can find no reference to his having investigated the area inside the line of cotton wool anaesthesia with any tactile hair exerting a pressure of more than 360 millegrammes which is about the normal threshold stimulus. As however he carried out his earlier investigations without the preliminary shaving which he later realised to be necessary for exact work, he did in fact accidentally use a stimulus far above the normal threshold. It had been shewn by *von Frey* 9 years earlier in his classical researches on tactile sensibility that the touch spots are localised in the region of the hair bulbs, and that these touch spots can be stimulated by pressure upon the skin near the hair or by movement communicated to the hair itself, and that the latter mode of stimulation yields sensations to a stimulus of much lower strength than does the former. *von Freys* says: „Ich habe schon in meiner ersten Mitteilung erwähnt, daß die schwächsten überhaupt noch wirksamen

Druckreize bei Berührung der Haare wahrgenommen werden. Die Schwelle des Haares liegt beträchtlich unter der seines Balges. So fanden sich z. B. für 6 bereits gekürzte Haare des Oberschenkels folgende Reizschwellen:

| Haar | Reizschwelle des Haares | Reizschwelle des Haarbalges |
|---|---|---|
| 1 | 1 | 12 |
| 2 | 3 | 17 |
| 3 | 5 | 12 |
| 4 | 5 | 12 |
| 5 | 5 | 12 |
| 6 | 5 | 33 |

Da nun die Reizschwelle des Haares sich um so mehr der seines Balges bzw. seines Druckpunktes nähert, je kürzer es geschnitten wird, um schließlich bei glatt rasiertem Haar mit letzterem zusammenzufallen, so muß man schließen, daß in beiden Fällen dasselbe Organ gereizt wird, vom Haare aus, der Hebelwirkung entsprechend, aber mit geringeren Kräften." (Beiträge zur Physiologie des Schmerzsinns. Zweite Mitteilung. Berichte über die Verhandlungen der Königlich Sächsischen Gesellschaft der Wissenschaften. 1895.)

We have ourselves obtained similar results. The following table is a characteristic example chosen from our records of such investigations.

*Normal skin of Left Forearm.*

| | | Stimulation of Hair Bulbs | | | | | | Stimulation of Hairs themselves | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Elastic pressure of *von Frey* hair in millegrammes | | 10 | 22 | 40 | 70 | 140 | 230 | 10 | 22 | 40 |
| No.: of Hair Bulb and Hair | 1. | o | o | X | X | X | X | At least 4 of the hairs reacted to this stimulus | X | X |
| | 2. | X? | o | o? | o? | X? | X | | o | X |
| | 3. | o | o | o | X? | X | X | | X | X |
| | 4. | o | o | X? | X | X | X | | X | X |
| | 5. | o | o | X? | X? | X | X | | o | X |
| | 6. | X? | o | X? | X | X | X | | X | X |
| | 7. | o | o | X? | o | X? | X | | X | X |
| | 8. | o | o | o? | o | X | X? | | o | X |

o denotes no sensation felt. X denotes sensation of touch felt.

It is therefore obvious that by stimulating the unshaved recovering area with cotton wool *Head* was applying a stimulus a good deal above the threshold of the shaved skin, hence as tactile sensibility was present only in a hypoaesthetic form, he got a reaction before shaving but not after. The reaction he got moreover shewed the characteristics which we have described as accompanying returning tactile sensibility namely intensification and peripheral reference. Furthermore in the earliest stages of recovery when he applied a much more intense stimulus by pulling the hairs, he was able to get a reaction 86 days after the operation. This corresponds closely with what we ourselves found in regard to the first appearance of tactile sensation in response to gross stimulation of a recovering area. Such stimulation for example yielded tactile sensations in two of our areas at 82 and 90 days respectively after the nerve section.

It seems to us therefore that the facts are capable of a simpler explanation than that offered by *Head*. In our opinion it is not possible to accept as established the supposed great delay in the return of tactile sensibility, or the equally remarkable acquisition by the hairs of a recovering area of the "form of sensibility independent of that usually called light cutaneous touch". That sensibility to tactile stimuli begins to return with the other kinds of sensibility and like them all in a hypoaesthetic form at first, is to our mind a well established fact and one accessible to complete methods of examination.

b) *Weber's Test.*

In *Head's* observations there was a close relation between tactile sensibility and the capacity to discriminate two simultaneous touches. Before recovery began he "was entirely unable to discriminate one from two points of the compasses even when separated for the widest distance permitted by the size of the affected area on the hand, 6 cm in a direction longitudinal to the axis of the limb. And yet over a similar part of the normal hand a perfect record was attained at 2 cm" (Human Experiment etc. p. 364). Moreover during recovery he found that this inability to discriminate the two compass points "except at distances enormously in excess of the normal" persisted until the return of sensibility to cotton wool stimulation.

There is considerable discrepancy between these observations and our own results. We found that discrimination was impossible only in areas of such profound anaesthesia that even firm pressure could not be felt, as for example over the inner surface of the tibia in the case of the Internal Saphenous nerve area. Outside such regions but within the boundary of anaesthesia to cotton wool we never found total loss of discriminatory capacity but merely a reduction of it so that an increase in the separation of the compass points yielded results which shewed a distinct degree of sensitiveness. For example the normal skin around one area responded to a separation of 25 mm; the skin in the zone of gradually deepening hypoaesthesia within the line of anaesthesia to cotton wool gave, with the same separation, results which were very poor. With a separation of 50 mm however the results were nearly as good as of those of the normal skin at 25 mm. Testing the same area of skin before and after section of the nerve supplying it was another method used. The area presumably supplied the by nerve which was to be cut was sub-divided into segments and each of these separately tested with the compasses. After the operation such of these segments as fell within the limits of sensory defect were again tested. One such segmentof the great auricular area gave before the operation out of 120 touches (single and double irregularly mixed) 84 right and 36 wrong: while after the operation it gave 75 right and 45 wrong. A segment fo the internal saphenous area similarly tested gave before the operation 85 right and 35 wrong and after the operation 72 right and 48 wrong. In both cases the separation of the compass points was the same throughout.[1])

[1]) During recovery the difficulty of compass testing is, as Head has pointed out, rendered very great by the phenomenon of reference which tends to make many of the single touches appear as double. Hence in the foregoing discussion we have not embodied any results of compass testing carried out on recovering areas.

Our observations then do not enable us to confirm *Head's* view that defects of tactile acuity and of discrimination of two simultaneous touches are always closely associated, or that sensibility to cotton-wool stimulation is invariably accompanied by inability to discriminate simultaneous touches. Section of a purely cutaneous nerve does undoubtedly diminish discriminatory capacity, but we have found time after time as the figures given above clearly shew, discrimination not very much below the normal in regions which were quite anaesthetic to stimulation with cotton wool. This conflict of evidence has led us naturally to examine somewhat closely the methods *Head* describes as having been used in his own case. His description is a detailed one and the precautions taken to exclude fallacy were numerous and stringent though it seems to us they were not altogether complete. In discussing methods of examination *Rivers* and *Head* say "Since *Head* was at the same time collaborator and patient we took unusual precautions to avoid the possibility of suggestion. No questions were asked until the termination of a series of tests; for we found it was scarcely possible in the long run to ask even simple questions without giving a suggestion either for or against the right answer. Sounds and movements that would have conveyed no information to an ordinary person would disturb *Head's* judgment in a case requiring fine discrimination . . . Towards the end of a series of observations with finer tests over an area of defective sensibility *Head* would frequently become uncertain in his answers because he had forgotten his sensations with the coarse forms of the same stimuli. He might for instance speak of contact with the neutral tube as warm. But occasional unexpected stimulation with the tube at 38° C would at once correct this tendency, and throughout the further observations the neutral tube would be recognised with certainty. After a long series of "double ones" the application of the compasses widely separated so as to produce a definite sensation of two points frequently produced a similar steadying effect" (Human Experiments etc. p. 345).

The latter paragraph indicates very well how great are the difficulties in securing the subject from receiving hints as to whether his answers are right or wrong. At first sight the procedure indicated might seem to one unaccustomed to such work comparatively harmless. A little consideration however will shew that the sudden interposition of a stimulus of unmistakeable intensity not only reminds the subject of the sensation-quality he has become uncertain of, but also acts as a signal informing him in the plainest possible terms that he is answering incorrectly. It is difficult to see how such signalling to the subject can be any less disturbing to the quality of the results than would be telling him in so many words that his answers were wrong. Indeed there is reason to suspect that the tendency to error would be greater than if the patient were clearly and simply warned that his responses were becoming grossly wrong. For not only are subject and investigator in a condition of false security as to the value of their methods but the information unwittingly given is suggesting in the case quoted not merely error in general but error in one special direction.

### c) *Thermal Sensibility.*

In regard to the restoration of sensibility to thermal stimuli there is a fairly close correspondence between *Head's* observations and our own. He observed the

phenomena of intensification and peripheral reference, the slower restoration of sensibility to temperatures above that of the skin, and the tendency of the intensification of heat sensations to cause stinging pain to replace true sensations of heat. He also observed that in the early stages of recovery the skin was a good deal less sensitive to temperatures near its own than is the normal skin. He did not regard this however as the expression of a mere hypoaesthesia, but adopted the more complex interpretation that it was due to the absence from the skin of a special mechanism solely concerned with the appreciation of temperatures covering a range of not more than 10 to 12 degrees centigrade of the thermometric scale. The remarkable nature of this hypothesis is rendered more evident when it is remembered that sensations elicited in the normal by temperatures within this range are extremely faint and that temperatures occupying about 5 degrees at the middle of this range can arouse no thermal sensation at all. It seems probable that *Head* did not realise the existence of this normal intermediate thermoanaesthesia, for he speaks of a "neutral point of thermal sensibility" as if he regarded the skin as capable of yielding an unbroken series of sensations corresponding with the thermo-metric scale. We shewed in 1909 that this was not the case, that there was always present in the normal an insensibility to temperatures within a few degrees of that of the skin and that the chief way in which a thermo-hypoaesthesia manifests itself is by an expansion of this intermediate zone.[1])

d) *Sensibility to Pain.*

In regard to the recovery of this form of sensibility there is a close general correspondence between our results and those of *Head*. He observed the phenomena of intensification, peripheral reference and the fact that in spite of the intense sensations which were yielded, the threshold was in the early stages abnormally high.

There is however one respect in which there is a considerable discrepancy between our results and his. He found that the phenomena of intensification and peripheral reference bore a remarkable relation to the return of tactile sensibility, in that when the latter had recovered so far as to yield sensations to stimulation with cotton wool the former underwent a diminution so rapid that he was led to assert that the return of sensibility to cotton wool caused the disappearance of intensification and peripheral reference. As we have already repeatedly stated in none of the seven separate experiments in nerve division which we made did we find that these two phenomena bore any such relation to the recovery of sensory acuity. In the areas where acuity was completely restored intensification and peripheral reference of tactile, thermal and painful sensations persisted for many months or years afterwards and faded very slowly without shewing any relation whatever to the other features of sensibility.

e) *Comparison of the Phenomena observed before and during Recovery.*

In the theoretical conclusions of *Head* great importance is attached to the resemblances he observed between the state of sensibility following upon the nerve section and that accompanying recovery.

[1]) In a recent paper "Sensory Disturbances from Cerebral Lesions", in dealing with normal thermal sensibility, Head no longer speaks of a "neutral point" but of a "neutral zone" which he defines as occupying from 2 to 5 degrees Centigrade of the thermo-metric scale.

As there is considerable discrepancy between his results and ours it is necessary for us to discuss the subject in some detail. According to *Head* section of a cutaneous sensory nerve produces (1) a central area in which there is loss of all forms of cutaneous sensibility and (2) a zone surrounding this in which the sensory loss comprises tactile sensibility, the capacity to discriminate two simultaneous touches and thermal sensibility for intermediate temperatures, that is to say temperatures between 26° C and 37° C. This region he calls the intermediate zone, and within it are retained sensibility to pain and sensibility to temperatures below 26° C and above 37° C. When he says that there is loss of tactile sensibility throughout the whole area (intermediate zone and central region) he takes loss of sensibility to cotton wool touches as the criterion of this and the line at which this loss occurs as the outermost limit of the changes found. Proceeding inwards from this line, he finds a narrow irregular zone in which, while there is insensibility to cotton wool, to intermediate temperatures and to *Weber's* test, there is sensibility to extreme temperatures and to pain. The pain sensations elicited here are abnormally intense, tend to be diffuse and radiating, abnormally unpleasant in quality and to cause the subject a scarcely resistible inclination to make some motor response such as withdrawing or rubbing the part.

The intermediate zone may be extremely narrow and may in places be absent altogether: in the latter case the whole area is insensitive to painful stimuli, the margins of insensibility to cotton wool and to pin pricks coinciding.

When recovery begins the intermediate zone gets larger at the expense of the central area which now begins to be sensitive to pin pricks and to extreme temperatures but remains for a considerable time (12 months) insensitive to cotton wool. The quality of the sensations elicited by pin pricks over regions in this first stage of recovery is the same as that previously felt in the intermediate zone. It is this identification of the sensory qualities of the recovering area and of the intermediate zone which forms one of the principal foundations of *Head's* hypothesis as to the constitution of the peripheral nerves.

The existence of this supposed identity we have been entirely unable to confirm.

It is clear that in order to be able satisfactorily to compare two sensory qualities, both of them abnormal, the subject should possess at one and the same time distinct areas due to the division of separate nerves in one of which recovery is in progress while in the other recovery has not begun. Unless this be possible either an undue reliance must be put on the memory of the subject, or there can be no certain guarantee that the sensibility in the part of the area supposed not yet to shew recovery is in fact entirely uninfluenced by regeneration. It has always been evident that the essential difficulty in accepting the more far reaching of *Head's* conclusions is that they are based upon a single experiment in nerve division and on the experiences of a single subject. We ourselves found that in investigating the effects of each one of the first six separate experiments which we made, we learnt many new refinements of technique and were able to take fuller and fuller advantage of the opportunities offered by each new area; and it was not until the seventh nerve section that we felt that our methods and experience were so thoroughly organised that we could use the final experiment as a confirmatory test for our previous

results. It should be remembered that the time at *Head's* disposal for the investigation of the changes following nerve section but preceding recovery, was limited to 6 weeks and that a very large amount of important and elaborate investigation had to be got through in this time. Now hyper-sensitiveness to painful stimuli following the nerve section and preceding recovery proved in our experience to be a very baffling phenomenon and one calling for much intricate investigation. To trace any uniformities in its occurrence and behaviour we found to be scarcely possible in connection with the first two nerves we divided and apart from learning that it certainly could not be generalised in the simple way indicated by *Head* we made little progress. With the knowledge gained by the later experiments certain uniformities did however become perceptible. Of these by far the most important and the most significant as regards its bearing on general principles was the fact that hypersensitiveness to pain in the area of the divided nerve was, when it occurred, essentially a transient phenomenon, always disappearing completely before there was any trace of recovery in the functions of the nerve, so that a quiet interval of at least a month was invariably to be observed before recovery began. In this interval there was never any trace of hypersensitiveness to pain. The affection of sensibility to pain now shewed a central area of profound loss surrounded by a zone of partial loss, the hypoalgesia being most marked towards the centre of the area and least marked at its periphery. We wish to state once more and with the strongest possible emphasis that during the quiet interval we have already defined this hypoalgesic zone never yielded sensations of pain either radiative or of abnormal unpleasantness. We have described elsewhere ("Experimental Studies" etc.) the details of the circumstances under which hypersensitiveness to pain may appear after section of the nerve. It is enough to say here that the distribution of it is always in irregular patches which shew an unmistakeable tendency to appear in the neighbourhood of subcutaneous veins and to have remarkably little relation to the distribution of defects in sensibility. It is not limited to the intermediate zone of *Head* and tends to overstep both the inner and outer margins of this but more especially the latter. The second fact of importance in this matter is that this irregularly patchy hypersensitiveness makes its first appearance about the 10th day after the operation, reaches its maximum in about a week and then begins to fade so that by the 6th week it can scarcely be detected anywhere and the characteristically stable condition of analgesia and surrounding hypoalgesia is definitively established. Thirdly by sufficiently delicate algometric observations a most important distinction can be made out between the transient hypersensitiveness to pain and the hypersensitiveness characteristic of recovery. The former is a true hyperalgesia that is to say has an abnormally low stimulus threshold, while the latter is merely an intensification of the response to stimulation and bears no direct relation to the degree of sensory acuity present at the time. Fourthly the sensations of pain elicited from patches of this transient hyperalgesia although abnormally unpleasant and tending to be somewhat diffuse have never in any single instance in our experience shewn anything in the remotest degree resembling peripheral reference. It will thus be seen that the whole of our experience gathered from two subjects and from areas in many different parts of the body is unable to afford the least support for the view that such hyperalgesia as occurs

before the appearance of recovery is in any way related to the intensification of painful sensations found in a recovering area.

The resemblances which he describes as existing between the intermediate zone and the early recovering area *Head* supposes to be due to these regions being supplied by a special set of nerve fibres which is concerned with sensibility to pain and to extreme temperatures. In any given nerve the fibres concerned with this group of sensations tend to supply a smaller area than that supplied with fibres which subserve sensibility to touch and to intermediate temperatures. Consequently when the nerve is cut the difference between the areas of the two kinds of nerve fibres is the intermediate zone, which is thus supposed to be an area of uniform sensibility of a special kind ("protopathic").

As we have already stated, in none of our experiments did we find such uniformity. On the contrary in each case we found that the region corresponding with the intermediate zone of *Head* was one of hypoaesthesia steadily increasing in degree when it was explored from the periphery towards the centre. So that for example while in the outer part the thermo-hypoaesthesia appeared as a slight increase of the normal indifference to intermediate temperatures, towards the inner part only the very faintest thermal sensations could be elicited with any temperature. There was therefore in our observations no evidence to encourage the belief that section of a cutaneous nerve can produce a specific and clearly marked loss of sensibility to temperatures from 26° C to 37° C. There is reason to suppose that *Head* was not at all advantageously placed for the investigation of the sensibility of the intermediate zone. In addition to the limitation of the available time imposed by the restriction of the work to a single experiment, it would seem that in his case, as it happened, the actual area of intermediate zone was extremely small. *Rivers* and *Head* say for example "In our case we had even less opportunity than usual for studying the primary dissociation of cutaneous sensibility. For on the anterior surface of the forearm the loss of sensation to prick and to cotton wool corresponded exactly. Towards the radial aspect its boundaries were ill-defined to both stimuli, merging gradually into parts of normal sensibility. But over the back of the hand lay a narrow border 2 mm in breadth insensitive to cotton wool but sensitive to prick" (Human Experiment p. 368). A region so limited as this cannot to our minds be regarded as capable of yielding altogether satisfactory results as to the true nature ot sensibility in the intermediate zone. It is true that another area presumably of intermediate zone type was discovered.

"Within three weeks of the operation (op. cit. p. 369) another small dissociated zone appeared in the first interosseous space around the distal border of the affected area. Here sensibility to painful cutaneous stimuli was so low that they were followed by no increased reaction. A prick produced a slowly developed dull aching different from the exaggerated discomfort evoked on stimulating the border on the back of the hand. Moreover this small area in the interosseous space was insensitive to all thermal stimuli and neither cold nor heat spots could be discovered within it. It was evidently so little sensitive to protopathic stimuli that the skin could respond to painful stimulation only and even this response was extremely feeble."

It is plain that this segment of the intermediate zone cannot have contributed evidence that the intermediate zone is endowed with sensibility to extremes of temperature and to pain, and that the sensations of pain elicited within it are abnormally unpleasant and accompanied by an excessive motor reaction.

Recovery occurs according to *Head* by the appearance throughout the area of the form of sensibility which is found after the operation in the intermediate zone. This is owing to the fact that the nerve fibres concerned with sensibility to pain and to extreme temperatures regenerate first. After these have completely regenerated there is a considerable pause and then the fibres concerned with sensibility to touch and to intermediate temperatures regenerate and restore sensibility to the normal. When this event occurs the characters peculiar to the first form of sensibility (intensification and peripheral reference) disappear owing to their being inhibited by the restoration of the second form of sensibility. Furthermore restoration of the second form of sensibility (touch and intermediate temperatures) may be incomplete leaving a part of the area permanently supplied with the first form of sensibility only. From such a statement of the facts our results shew divergences which seem to be essential. Most of these have already been stated but it is necessary that we should add something here on the subject of incomplete recovery. Incomplete recovery is undoubtedly common but the evidence we have accumulated shews that there is no special tendency for sensibility to return in two well defined groups or for one group to return alone. If owing to incomplete recovery some part of the area remains permanently hypoaesthetic there is no tendency for the hypoaesthesia to touch to be particularly marked. Moreover in a large area some part may shew a permanent failure of recovery of all forms of sensibility. *Failure of recovery then, according to our observations, is in no sense selective for different forms of sensibility, and appears in such a way as to suggest that it is due to some general obstacle to regeneration rather than to a hypothetical difference in regenerative energy possessed by nerve fibres of different functions.* The impression that sensibility to pain and to extreme temperatures, specially cold, recover earlier than sensibility to touch might very easily be gained even after a fairly thorough examination because the picture presented by a recovering area is dominated in so remarkable a way by the phenomena of intensification and peripheral reference which are especially marked for sensations of cold and pain. As we have already seen the apparent delay in the restoration of sensibility to heat is probably due to the exaggeration of the pain factor in the sensation "hot" by intensification, and we have pointed out that similar qualities in returning sensibility to touch led *Head* to assume the existence of a hypothetical "hair sensibility". It would seem that intensification and peripheral reference must be dealt with as phenomena unrelated to the recovery of sensory acuity for we found no evidence that they underwent any sudden and striking diminution when an area recovered sensibility to cotton wool touches, but might be recognisable years after this period. We cannot therefore confirm *Head's* attempt to identify them with special forms of sensibility and we could find no evidence of their being "inhibited" by the reappearance of any other form of sensibility. So little in fact is peripheral reference inhibited by returning sensibility to touch, that touch sensations themselves shew the phenomenon in its most exquisite form.

**Head's hypothesis of the constitution of the peripheral nerves.**

However great may be the differences between the observations of *Head* and of ourselves and we have shewn above that they are considerable, the fact is established by both series of investigations that during recovery after section of a cutaneous nerve, the affected area shews certain very remarkable peculiarities of sensibility. These peculiarities can as we have shewn be narrowed down to the phenomena of intensification and peripheral reference. In addition to their directly practical importance intensification and peripheral reference are matters of great theoretical interest. To the subject of them they present a series of sensations entirely new and altogether outside his previous sensory experience, and yet they are surprisingly definite and unmistakeable. No one who has not experienced them can appreciate the intense vividness with which they present themselves to the subject; and the investigator with no direct knowledge of them is likely even to be wearied by the importance their brilliance makes them assume in the subject's mind.

It has been suggested by authorities whose opinions are entitled to very respectful consideration (*von Frey, Mackenzie*) that these peculiarities of recovering sensibility are of central origin and possibly due to changes in the central nervous system consequent upon the nerve section. It is clear that this possibility is one which should not be overlooked but it must be admitted that at the present time but little positive evidence bearing upon it has been accumulated.

The hypothesis which has been put forward in the greatest detail is that of *Head* who first observed the phenomena under experimental conditions. This hypothesis was first enunciated in 1905 in a paper containing a summary account of observations upon an area of sensory loss experimentally produced upon the writer's arm. It was expounded in greater detail in a paper dealing with the same observations in 1908. Not long after, our own observations were also published. Although it was clear that there were profound discrepances not only between the interpretations but also between the facts as recorded by *Head* and ourselves, we felt that a detailed criticism of *Head's* hypothesis would then be premature and contented ourselves with pointing out some of the more obvious difficulties in accepting some of his facts and many of his conclusions. Since that time the divergences between our views and his have in no essential particular diminished and no evidence has been produced which seems to us to disprove or to explain away the observations we then described. It seems therefore desirable to take advantage of the opportunity now presented to attempt some more fundamental criticism than we have yet entered upon. A short exposition of *Head's* hypothesis is first necessary. According to him the skin is supplied by two distinct systems of nerves which endow it with

1. "Protopathic sensibility capable of responding to painful cutaneous stimuli and to the extremes of heat and cold. This is the great reflex system producing a rapid widely diffused response unaccompanied by a definite appreciation of the locality of the spot stimulated.

2. Epicritic sensibility by which we gain the power of cutaneous localisation, of the discrimination of two points and of the finer grades of temperature called cool and warm."

According to this view the peculiarities of the early recovering area are due to the fact that it is innervated solely with protopathic nerves which regenerate more easily and more rapidly than the epicritic. As soon as epicritic sensibility returns, which is several months later, the peculiarities of the early recovering area disappear. As *Head* says (Human Experiment p. 448) "When once a part of the body is endowed with epicritic sensibility reference ceases entirely." Any given cutaneous nerve tends to supply epicritic sensibility to a larger area than that to which it supplies protopathic sensibility. Consequently when the nerve is cut the area of epicritic loss is larger than that of protopathic loss and consequently there is a region more or less extensive inside the boundary of epicritic loss which is still supplied with protopathic sensibility. This is the intermediate zone and as it is possessed of protopathic sensibility the sensations elicited from it are essentialy the same as those elicited from an early recovering area. Protopathic sensibility is of a more primitive and less developed nature than epicritic sensibility and represents an earlier stage in the developmental history of the nervous system. There is one area on the surface of the body, the glans penis, which is normally endowed with protopathic sensibility only. The internal organs are supplied with protopathic sensibility and the referred pain which is sometimes met with in visceral disease is a phenomenon of the same order as the peripheral reference of a recovering area. It is a simple corollary from this hypothesis that the intermediate zone after nerve section, the early recovering area, the glans penis and the viscera are all endowed with sensibility of the same type and that the sensations elicited from them are in essence of identical characters.

The detailed exposition of the hypothesis does not present quite so symmetrical an appearance as do the general statements. For example the insensibility to intermediate temperatures presented by a protopathic area is sometimes referred to as ranging from 22° C to 40° C and sometimes as ranging from 26° C to 37° C; areas described as protopathic may be totally destitute of thermal sensibility, or while sensitive to cold may be insensitive to heat. Again it appears that protopathic sensibility is not entirely devoid of the capacity of responding to light touches, for comparatively early in recovery the hairs of the "protopathic" part were found to react to cotton wool. It is denied that this is sensibility to light touches and a special form of "hair sensibility" is postulated and assigned to the protopathic system. With regard to the reference of sensation the preciseness of the phenomenon as it occurs in the recovering area is brought out. In the intermediate zone however and on the glans penis there is no description of any precise reference and the sensations are merely described as being diffuse and no remark is made upon the total difference between the two conditions.

In view of these frequent slight ambiguities, no doubt merely in expression, the hypothesis when viewed in direct relation with the evidence acquires a certain indistinctness which renders closely reasoned criticism somewhat difficult.

In judging the acceptability of a hypothesis such as this it is necessary to keep clearly in mind that the considerations supporting it are derived from two entirely different sources which yield evidence of very different value. These different qualities of evidence may be described as the direct and the indirect. By the direct evidence we mean that collected under the specially favourable con-

ditions of the actual research itself from which, it may be supposed, the hypothesis was a conclusion inductively drawn. Clearly such evidence is of far greater value than any other and criticism of it must be directed either to the facts of observation or to the processes of induction leading to the hypothesis itself. By indirect evidence we mean the various corroborrative applications of the hypothesis to facts not directly observed during the research, to supposed matters of common knowledge or to other speculative conclusions. This second class although of notoriously slight evidential value is as is well known apt to acquire undue importance in influencing one's judgment in favour of a given hypothesis. It is therefore of great importance that this type of evidence should be dealt with separately in the full realisation that its influence is usually in excess of its value.

In dealing with theoretical considerations concerned with the physiology of the nervous system, one is exceptionally liable to be misled by preconceived or introspectively evolved notions as to how sensory and perceptive processes may be supposed to act. Symmetry and the desire for classification are apt to be mistaken for physiological principles and we tend to drift into the error of supposing that conceptions which are clear cut, easily comprehensible and "reasonable", acquire by that very fact an increased probability of being accurate expositions of the physiological processes they profess to explain. This has been repeatedly demonstrated in the history of neurology. A very good instance of it is shewn in the development of the theory of aphasia. The earlier workers on the subject evolved from the study of such of their mental processes as were accessible to introspection certain very definite conceptions as to how the processes underlying the mechanism of speech must work. Gradually a series of conceptions grew up which derived their chief support not so much from contact with the facts of cerebral pathology as from their inherent reasonableness, and it is quite lately that we have begun to learn that physiological necessity is apt to defy our preconceived notions of resonableness and to escape any classification which is more respectful of logic than of fact.

When *Head* advances the conception of two forms of peripheral sensibility one more primitive than the other and forming the sole sensory endowment of an earlier type of organism, the idea is at first sight attractive. We are presented with a picture of a creature of simple needs, possessed of a sensorium capable only of informing him of powerful stimuli, these stimuli leading to bulky sensations which call imperatively for immediate reaction. With further development and increasing need for communication with the environment the second form of sensibility appears, which while endowing the higher animal with the capacity for appreciating more delicate stimuli inhibits the now unnecessary and harmful energetic reaction to stimulation to which he was previously liable. The whole conception is striking and ingenious but carries with it no internal corroboration. Scientific criticism cannot regard it as making in any degree the existence of the two hypothetical forms of sensibility more probable. We have no evidence that one form of sensibility is biologically more primitive than the other, the sense of contact given by tactile sensibility is as far as we know just as essential as the sense of pressure obtained in the absence of it. While if we are to accept *Head's* view that peripheral reference is an essential part of protopathic sensibility it is difficult to conceive

a more dangerous endowment for any animal however primitive than the capacity to feel when it is injured a sensation of pain in some part of the body remote from the lesion.

On the other hand there are certain inherent difficulties in the acceptance of the hypothesis which cannot be overlooked in any general consideration of it. For example the whole problem is dealt with on the assumption that all the phenomena consequent on a section of the nerve whether they occur before or during regeneration are entirely those of loss of function. That the destruction of the nerve after it has been severed from its centre produces no effect upon the tissue in which it lies except the loss of sensibility and that the reinvasion of the affected area by the regenerating nerve produces no effect upon the invaded tissues except a restoration of sensibility seems to us a large and serious assumption which should not be made without critical enquiry.

Again the multiplication of sensory mechanisms assumed by the hypothesis is a feature upon which criticism may well be directed. The difficulty is sufficiently great when we find thermal sensibility divided between two entirely different mechanisms, the one dealing with temperatures between 26° C and 37° C, the other with temperatures outside this range. The difficulty seems even greater with regard to sensibility to touch; for we find that while ordinary tactile sensibility belongs to the epicritic system a peculiar form of "hair sensibility" also aroused by light touches, belongs to the protopathic system; so that while in the case of thermal sensibility the protopathic and the epicritic systems have distinct end organs of their own, with regard to sensibility to touch they both use the same end organs.

Such theoretical objections might be developed to a much greater extent but they are of secondary importance as compared with the criticism of the direct evidence upon which obviously the case must ultimately rest.

The facts of observation which form the basis of the hypothesis fall into two categories; first those derived from the study of an area of sensory defect experimentally produced, and secondly the occurrence normally of an area of skin which is supposed to be endowed with protopathic sensibility only. Of the facts of the first category, three are absolutely fundamental and upon the authentication of them the establishment of the hypothesis depends. These are:

1. The identification of the sensory conditions found before the beginning of recovery in the intermediate zone with those found in the early recovering area.

2. The absence of recovery of tactile sensibility during the period when sensibility to pain and to extreme temperatures is being restored.

3. The fact that the phenomena peculiar to sensibility in the early recovering area, namely intensification and peripheral reference are abolished by the restoration of tactile sensibility as measured by cotton wool stimulation.

We do not propose to recapitulate the evidence we have produced above in criticism of the validity of these supposed facts, but we may add a few words in general comment.

Our investigations were undertaken primarily with the desire of confirming *Head's* conclusions by the use of the method through the introduction of which he had so greatly enriched the resources of experimental physiology. Inclined as we were to accept his conclusions we felt that being founded upon a single experi-

ment, they could not be fully recognised without further experimental confirmation. It was only after the earlier experiments and when we had come to see that the attempt to reconcile the facts we were collecting with the principles of *Head* was leading to increasing difficulty and confusion, that we realised that the hypothesis put forward by him was not capable of generalising the facts.

It will be remembered that we have produced a good deal of evidence against the acceptability of each of the three facts we have enumerated above as fundamental to *Head's* conclusions, and we have shewn incidentally in many cases the probable mechanisme by which he was led to what we regard as incorrect inferences.

We now have to deal with the second group of facts of observation namely that based upon the sensory peculiarities of the glans penis which according to *Head* is a part of the body endowed with protopathic sensibility only.

In 1895 *von Frey* had fully described the sensibility of the glans penis. He found that the glans was insensitive to tactile stimuli, sensitive to painful stimuli and to a certain extent sensitive to thermal stimuli. The thermal sensibility was marked at the neck and corona of the glans but diminished rapidly from there towards the end of the organ to reappear in the neighbourhood of the meatus; midway between corona and meatus it was practically altogether absent. The frenum and the inner aspect of the prepuce had the usual sensibility of the skin. The pain elicited by appropriate stimulation over the glans was especially unpleasant and of a deep seated boring character. The thermal sensations at the neck and corona were very distinct. *Head* confirmed these results and added that such parts of the glans as had any thermal sensibility, namely the corona and immediately round the meatus, though sensitive to extreme temperatures were insensitive to intermediate temperatures. He concluded that the glans penis is, in addition to deep sensibility, endowed with protopathic only, and regarded it as a remarkable confirmation of his hypothesis that there should occur normally an area of skin where owing to the absence of epicritic sensibility the existence of protopathic sensibility was disclosed. We have already referred to the variability in the conditions to which the term protopathic sensibility is applied and this is to some extent a case in point. The fact that painful sensations produced by stimulation of the glans are described as deep seated and felt as if in the urethra is apparently taken as comparable with the phenomena of reference in a recovering area. Now one of the most striking facts about the latter phenomenon is that the referred sensation is invariably superficial and of a remarkably definite localisation. It is always possible for the subject to point with his finger to the exact spot where the referred sensation is felt. Again nothing is said about any similar reference of thermal sensations but if there is one fact more striking than another with regard to thermal sensibility in a recovering area, it is the extraordinarily vivid reference of sensations of cold. It would therefore be necessary to sacrifice the most striking peculiarity of "protopathic" sensibility if the sensibility of the glans penis were to be brought within that category. Supposing however that such objections could be overruled it may yet be asked whether we are justified in accepting the explanation put forward by *Head* of the sensory character of the glans penis or whether an explanation more consonant with the general body of physiological knowledge can be found.

Let us briefly recapitulate the facts. The glans penis is insensitive to touch but sensitive to pain; its general surface is insensitive to thermal stimuli but its margins are sensitive to them. Such thermal sensibility as is present however is of a diminished acuity, for we learn that even in what we may call the marginal regions (the corona and immediately round the meatus) intermediate temperatures are not appreciated. To explain such peculiarities the most obvious course would seem to be an enquiry into the embryological history of the part. Now the penis is completely formed and intrauterine life is far advanced before the prepuce is differentiated; there then begins near the meatus the ingrowth of a solid lamina of epithelium which cuts off the prepuce from the glans. This ingrowth of epithelium subsequently splits into two lamellae setting free the prepuce and furnishing the epidermal lining to it and the covering of the glans. The process is remarkable as occurring so late in foetal life; in fact it is frequently incomplete for some time after birth as shewn by the occurrence of the well known "adhesion" between prepuce and glans. This detachment of the skin of the glans at so late a period may well be supposed to exercise a profound effect upon the sensibility of the latter, and there is a remarkable coincidence between the distribution of this separation and that of the sensory peculiarities. The process begins around the meatus, therefore the actual neighbourhood of the meatus itself is unaffected; it is arrested at the corona and at the frenum so that the frenum and the parts central to the corona are of normal sensibility. Finally in the regions near where the process begins and ends (meatus and corona) we find thermal sensibility surviving for a short distance in an imperfect form. In face of an explanation so extremely simple we do not feel that it is necessary to invoke an hypothesis involving the whole structure of the peripheral nervous system to explain the sensory peculiarities of the glans penis.

**On the significance of the phenomena observed during the recovery of sensory nerves.**

When we published our observations in 1909 we did not feel that the facts justified our going in the direction of attempting to explain the peculiarities of recovering sensibility beyond hinting that the evidence seemed to point to some local peculiarity in the regenerating nerve trunk. Further experience and reconsideration of the facts seem now to justify some more definite expression of opinion. We may say at once that though certain modifications in our statement of some of the elements of the problem have become necessary, our opinion of the direction in which the solution lies has been confirmed. Any discussion of the matter to be at all effective must be prefaced by a statement in the clearest possible terms of the phenomena it is concerned with.

### 1. Facts of Observation.

During the process of recovery after section of a cutaneous nerve three groups of remarkable phenomena are to be observed. Two of these are concerned with sensibility in the recovering area, viz Intensification and Peripheral Reference. The third concerns the recovering nerve trunk between the point of section and the proximal boundary of the affected area. It consists in the possession by this length of nerve of a greatly increased accessibility to direct stimulation.

a) *The facts of Intensification.*

By intensification we mean that qualitative change in the sensations elicited from a recovering area which makes them abnormally vivid. The vividness is most marked in sensations of cold and sensations of pain and less marked in sensations of touch and sensations of heat; the difference probably does not indicate more than that the sensation of touch is by nature but little susceptible of magnification and the sensations of heat when intensified tend to be felt principally or wholly as pain. Intensification is intimately associated with peripheral reference in such a way that an intensified referred sensation may alone be felt, or may be felt in association with an intensified local sensation. Intensification frequently accompanies defects in sensory acuity but on the other hand it always persists long after sensory acuity is completely restored. For example, one area five years after section of the nerve and four years after restoration of sensory acuity, still shews intensification. The fact that the phenomenon is present throughout the whole period of recovery may lead to confusion in description unless this is especially guarded against. For example in the early stages of recovery when the threshold for pain is still high it would obviously be incorrect to describe the area as hyperalgesic however unpleasant the sensations elicited might be. On the other hand when the pain threshold has come down to the normal and a stimulus which just produces pain in the normal skin, produces a much more intense pain on the abnormal, the latter might fairly be described as hyperalgesic. In our earlier contribution we did in fact describe it as such but we now think that the use of the term hyperalgesia is better avoided in this connection because it is accurate only during a certain period of recovery. Even when pain can be elicited by a stimulus that does not cause pain on the normal skin as is the case when heat stimuli are used at a certain stage, it is safer not to use the term hyperalgesia otherwise the impression is given that there is a closer relation between sensory acuity and intensification than really obtains.

b) *The facts of Peripheral Reference.*

We use the term peripheral reference to indicate the peculiarity of recovering areas whereby sensations, instead of or in addition to being felt at the place stimulated, are felt in the distal part of the affected area. It is the earliest phenomenon of recovery and is characteristic of the first sensations of recovering sensibility such as can be elicited only with strong stimuli applied over the point where the nerve trunk enters the affected area. It is moreover the most persistent result of the nerve section, surviving years after the complete recovery of sensory acuity. In this respect it corresponds exactly with intensification with which it is very closely associated, for all sensations capable of intensification when they are peripherally referred are intensified. All sensations are capable of peripheral reference though all do not shew it with equal readiness. It is a very precise phenomenon for sensations of touch, of cold and of pain but it is difficult to demonstrate in regard to sensations of heat. If the investigation is limited to stimulation with metal cylinders having a small surface of contact (1 mm in diameter) it may be impossible to demonstrate peripheral reference of heat, because intensification causes the thermal factor in the referred sensation to be obscured by the pain factor. It was for this reason that in our earlier contribution we stated that we had been

unable to observe peripheral reference of a clear sensation of heat. Later investigation has shewn that with the use of a large stimulating surface heat sensations are found to behave as regards reference as do cold, touch and pain.

At an early stage, on stimulation of a given spot the referred sensation alone is felt and there is a total absence of any local response. Later a local sensation is felt in addition to the referred and both are equally clear and equally intensified. Very gradually the intensification of both diminishes but up to the present time none of the areas upon which we experimented has altogether lost peripheral reference. In a general way it may be stated that the seat of the referred sensation, to whatever part of the area the stimulus may have been applied, is somewhere in the most distal part of the region rendered anaesthetic by the nerve section. It always extends up to the margin of the area. Now when a cutaneous nerve in one of the limbs is cut the area of anaesthesia produced usually tapers towards its distal extremity so that the region in which peripherally referred sensations are felt tends to be much narrower than the more proximal parts of the area. The consequence is that all the peripherally referred sensations are felt in the same spot. When the area happens to have a relatively broad distal extremity it can be shewn that the reference though always distal may to a certain extent be diagonal as well. For example in the case of the internal saphenous where the whole area is of great breadth stimulation of the anterior part of the area elicits a sensation referred to the back of the malleolus while stimulation of the posterior part of the area elicits a sensation referred to the front of the malleolus. In the case of the great auricular nerve however the area of skin supplied is distributed with its long axis at right angles to that of the nerve; peripheral reference here therefore shews this spreading of the foci of reference very clearly and spots can be found along the margin of the area to each of which sensations are referred from some special part. A character common to all cases is that the actual region to which sensations from a given part of an area are referred is always considerably smaller than the area the stimulation of which yields the sensations. These statements as to reference to small and distinct foci are true only so long as the stimulus used is not more than moderately energetic. When the energy of the stimulus is greatly increased, by increasing the area to which it is applied, the referred sensation spreads so as to occupy the whole nerve area distal to the point stimulated. The phenomena of peripheral reference are always to be obtained in their most marked form in the near neighbourhood of the regenerating nerve. The facts of reference given thus far are relatively simple and the statement of them includes all the most striking phenomena.

There is however a further statement to be made in regard to a group of facts which are much less conspicuous. When the process of recovery has reached the distal half of a given area it is found that many of the sensations elicited by stimulation here are referred proximally. These proximally referred sensations are much less distinctly intensified than those peripherally referred and are felt to some extent along the course of the regenerating nerve but chiefly at the point of nerve section. This phenomenon is especially striking in the one case in which the point of nerve section was no less than 6 inches proximal to the upper limit of the affected area. At the stage when proximal reference has appeared stimulation of many

a spot in the distal part of the area will yield three distinct sensations namely local, peripheral and proximal. A similar spot may also yield a proximal sensation alone or peripheral and proximal sensations alone. It may be remarked in this connection that in the case of the great auricular nerve although proximal reference to the point of section was never observed, there were many spots which yielded sensations referred to two distinct regions such as one on the cheek and one on the ear.

c) *The facts of Increased Excitability of the Nerve Trunk.*

The third important group of phenomena accompanying recovery is that concerned with the increased excitability of the nerve trunk. Certain cutaneous nerves run a long superficial course before they reach the region to which they are distributed. Such a nerve as we have pointed out elsewhere can be localised and traced with great exactitude by exploring the surface of the skin with the faradic current. If the course of the nerve be ascertained and marked on the surface by some relatively permanent stain such as silver nitrate, a more or less extensive length of it between the point of nerve section and the proximal limit of the consequent anaesthesia will be available for investigation during the period of recovery. It will then be found that the regenerating nerve trunk responds to stimulation some time before the skin to which it is distributed has regained any of its sensibility.

In order that such investigation shall be satisfactory it is obvious that two conditions must be satisfied. First that the nerve must be subcutaneous so that it shall be accessible to stimuli of moderate energy and secondly that its course between the point of section and the point where it begins to be distributed to the skin shall be long, so that it may be certain that responses are due to stimulation of the nerve and not to stimulation of its end organs in the skin. In one experiment as already mentioned we were so fortunate as to find and divide a nerve (middle cutaneous of thigh) which had a superficial course below the point of section of as much as 6 inches before it began to be distributed to the skin. The nerve had been marked out on the surface before the operation so that during recovery we had an exceptionally good opportunity of investigating its sensibility under the most favourable circumstances. Investigation of this nerve shewed not only the earliest evidences of recovery but that it acquired as regeneration progressed a very remarkable increased accessibility to direct stimulation. The sensations elicited by stimulation of it were invariably referred to the area of distribution. If the stimulation was moderate the sensations were referred to the peripheral part of the area. Energetic stimulation however led to the sensations being felt throughout the whole area and possibly along the nerve trunk itself as well. This increased excitability was limited to the nerve below the point of section and never extended above it. The stimuli which were effective were the faradic current, touches, pain stimuli (thermal or mechanical), heat and cold. The specific quality of the sensation elicited by the various stimuli was perfectly clear and shewed intensification which was distinct but not so pronounced as that found in the recovering area itself. The specific quality was most unmistakeable of course in the case of cold, this being of all sensation, the one which is qualitatively the most characteristic. The latent period between the application of the stimulus and the perception of the sensation was in the case of cold of considerable length because of the time occupied

in the transmission of the thermal change through the skin. As might have been expected the results of stimulation with heat were more difficult to obtain and more elusive. Nevertheless they were perfectly definite and we are able to state that stimulation of a regenerating nerve with heat produces corresponding sensations in the recovering area.

The increased excitability of the nerve reached a very high grade so that for example ordinary punctate stimulation with cold easily produced typical sensations.

d) *On the excitability of normal nerve trunks.*

We have referred to these remarkable changes in the nerve trunk as an increased excitability rather than as an altogether new property of the regenerating tissue because it is an old observation that normal nerve trunks are excitable though to a much slighter degree. The observation upon which this knowledge is based seems to be the statement that if the elbow be held in iced water sufficiently long a sensation of cold will be felt in the area of distribution of the ulnar nerve. The observation does not seem to have been repeated very often and one may well suppose that it has proved discouraging, for the conditions of the experiment are as bad as they could well be. The nerve is not really subcutaneous so that the immersion of the part in iced water would have to be prolonged to produce the desired effect. Such prolonged and extreme cooling would lead to a local aching in the part intense enough to disturb the critical capacity of the most philosophic. If however subcutaneous nerves are chosen in a part comparatively free from fat, clear results can easily be obtained. The nerve we have found most suitable for the experiment is the musculo-cutaneous of the leg. In front of the ankle and on the dorsum of the foot the branches of this nerve can be readily seen and felt so that stimuli can be applied to them with certainty. There is therefore little or no difficulty in demonstrating that the nerve trunk is sensitive to stimulation with cold and that the resulting sensations are felt according to the energy of the stimulus in the peripheral part of or throughout the area of distribution. The only other stimulus to which normal nerves at all readily respond is the faradic current. As this stimulus is very much more easily conducted through the skin than is a thermal change many more nerves can be got to respond to it than can be stimulated by cold. If the current used be weak the sensation resulting is a painless fluttering in the distal part of the nerve area. Strong stimulation gives a heavy drawing vibration throughout the whole area which although a sensation of great "bulk" has surprisingly little of the specific quality of pain.

The question whether stimulation of a normal nerve trunk with heat can call forth corresponding sensations in the area of distribution is obviously of considerable interest. It is however by no means easy to decide and we are not in a position to give a definite answer. The most we have obtained has been a very vague sensation of warmth, of all sensations perhaps the most difficult for the subject to be sure of.

The whole matter of the excitability of sensory nerve trunks seems to have escaped the amount of attention it undoubtedly deserves and, considering the simplicity of the necessary procedures, should obtain. We have not been able to give to it any detailed study but have had to content ourselves with demonstrat-

ing that the peculiarities of excitability possessed by a regenerating nerve are merely those of the normal nerve exaggerated to a marked degree[1]).

## 2. Theoretical Considerations.

In attempting to elucidate the meaning of the various remarkable phenomena which are found in connection with recovery after section of a cutaneous nerve it is as we have already said important to pay particular attention to the facts in their general physiological bearing and not to regard them too exclusively from the purely neural point of view. In our earlier contribution we pointed out that section of a nerve leads to the appearance of certain phenomena which cannot be ascribed to a mere loss or diminution of sensibility however specialised and must be regarded as being other than purely neural manifestations. In the same way it would seem that during recovery there are processes at work other than the mere growth of the new nerve fibres along the connective tissue residue of the degenerated nerve.

The phenomenon of peripheral reference is at once one of the most striking and perplexing features in the process of recovery. In our former paper we were not able to go further by way of interpretation than to suggest that it must depend on some peculiarity of the regenerating nerve. We are now able to shew reason to believe that when a stimulus causes a sensation to be felt not at the point of application but in the area of distribution of the nerve the significance of the reaction is that the nerve fibres themselves have been stimulated. We have shewn that the fibres of a nerve trunk are capable of reacting to the five kinds of stimulus and of yielding sensations of the corresponding specific qualities. This property is difficult to demonstrate in normal nerves for some forms of sensation, those most difficult to elicit being pain and response to mechanical stimulation and heat. The capacity of reacting specifically to all kinds of stimulation is however possessed fully and unequivocally by the regenerating nerve, in regard to which it can be demonstrated under suitable circumstances with great ease and unmistakeable precision. In both cases the sensations are invariably referred to the distribution of the nerve. *These observations shew then that conducting fibres of a peripheral nerve are capable of originating when appropriately stimulated, the five specific sensations*[2]). The sensations thus aroused differ from those originated in the skin in one character only namely localisation. Even in the case of the trunks which have remained abnormally excitable for several years we have found no evidence that nerve fibre stimulation can yield a local sensation. As long as it is felt the sensation is invariably referred to the area of distribution, to the peripheral part of it if the stimulus is moderate, to the whole of it if the stimulation is strong. Now it is obvious that there is a remarkable resemblance between the phenomena of nerve fibre sensibility and those of peripheral reference as found in the recovering area. In the latter

[1]) One other change noticed in the recovering nerve was a very considerable thickening. Whenever the nerve lay in a part free from subcutaneous fat this change could be observed and the nerve became visible far down into the recovering area.

[2]) The five specific sensations referred to here are course touch, pain, heat, cold and that produced by faradic stimulation. The first and the last are for convenience regarded as distinct though they resemble one another very closely. In the case of the regenerating nerve in fact the referred sensation produced by a weak faradic current and that produced by a firm stroking of the skin are almost indistinguishable.

at an early stage of recovery all sensations are referred and no local response is elicited. With a moderate stimulus the referred sensation is felt at some part of the periphery of the area, when the stimulation is energetic the sensation is felt throughout the area distal to the point stimulated. It may fairly be concluded therefore that the phenomena of peripheral reference are due to something in the nature of nerve fibre stimulation. If this conclusion be justified it leads to the further proposition that *in an area where recovery is in progress the regenerating nerve fibres shew a greatly increased accessibility to direct stimulation.* This increased excitability is such as to yield a characteristic response even in the parts of the area which lie at a distance from the nerve trunk although the response is of course to be obtained in its most impressive form from stimulation applied in the immediate neighbourhood of the nerve.

As recovery proceeds a time arrives when a given spot which previously has yielded peripherally referred sensations only, begins to give a local response. It is difficult to resist the conclusion that the appearance of local sensibility is due to the reestablishment of the connection between nerve fibre and end organ. If this were the case it would be of interest as indicating that the function of the end organ is to do with localisation rather than with acuity. In regard to the function of end organs in general three hypotheses present themselves. First that these structures are concerned with the conversion of specific stimuli into specific nervous impulses, so that for example there would be a series of end organs concerned with deriving from the physical process of heat loss the special sort of nerve impulse which originates sensations of cold. Secondly they may be supposed to be concerned with acuity of sensation, acting so as to magnify or modify the physical processes underlying sensation. Or thirdly as we have suggested they may be mainly or exclusively concerned with the localisation of sensation to the point stimulated. With regard to the first supposition the evidence we have produced as to the specific sensibility of nerve fibres shews that there is no physiological need for end organs to render the physical processes of stimulation capable of originating specific impulses in the nerves. With regard to the second possibility we have found that nerve fibre sensibility is capable of reaching a high grade of sensitiveness. Areas which yield nothing but peripherally referred sensations may come very near the normal threshold of acuity. That they can reach it is difficult or impossible to demonstrate because just as they are approching this degree of sensitiveness local sensibility begins to appear and although the phenomena of reference continue it cannot be proved that the increase of acuity to the normal is not due to the mechanism which endows the part with local sensibility. Nevertheless the evidence derived from the facts of recovery seem to us to point against the view that the end organs, so called, are essentially concerned with sensory acuteness. It does not seem that the relation between the anatomical distribution of end organs and variations in sensibility has been at all accurately established, many parts of the body for example being richly supplied with these structures but possessing sensibility of a very low grade or of a much simplified kind. The case of the cutaneous end organs for touch on hairy parts is somewhat peculiar in that the hairs by their lever action very obviously have a magnifying effect upon the physical disturbance which they transmit to the nerves.

The view that the acquisition of local sensibility is in some way concerned with the relation of nerve fibre and end organ must not be regarded as more than quite tentative. We are aware of many difficulties in the way of accepting it such for example as the presence of end organs where localised sensation is not experienced, e. g. serous cavities. The collateral evidence however of the existence of some mechanism which enables nerve fibre sensibility to be converted into local sensibility is sufficiently strong to lend a certain prima facie plausibility to the suggestion. We shall have occasion to refer later to another possibility as to the function of some of these end organs.

We may now consider what explanations can be offered of the very great increase in accessibility to direct stimulation shewn by the nerve fibres of the recovering area. Before making the attempt we would emphasise once more the fact that we have to do with an increase of a normal characteristic of nerve fibres rather than with the appearance of a new one. As we have shewn normal nerves possess the same character to a slight extent, regenerating nerves shew it to a more marked extent, while it reaches its fullest development in the recovering area itself. Two principal lines of explanation present themselves. First that the nerve fibres themselves may be in a condition of increased excitability and secondly that they may be physically more accessible to stimulation. In dealing with these possibilities it will be convenient to take into consideration the phenomena of intensification as well as those of peripheral reference. It is clear that there is some close association between the two. They appear together in the early period of recovery, they are both manifested by the regenerating nerve trunk and by the recovering area and they both persist until long after recovery of sensory acuity is complete. As might be expected it is usually easier to demonstrate reference than intensification at a very late period because the demonstration of the latter depends upon a quantitative estimation which may be difficult when the abnormality is slight, whereas the former as long as it is present at all is easy to recognise. Intensification it will be remembered may be a character not only of peripherally referred sensations but also of sensations felt locally. It is however most marked in referred sensations and rarely reaches such a degree in local sensations. It also tends to disappear from the latter sooner than it does from the former so that it seems that with the acquisition of locality something has occurred which, while not abolishing intensification tends to allow of its subsidence. Hence it appears probable that intensification is favoured by the conditions which allow of nerve fibre sensibility or is a direct consequence of that phenomenon. We have seen that the intensified sensation is an exaggerated response to stimulation and does not signify necessarily an increased sensitiveness; hence it may be present in a region of hypoaesthesia or in a region of normal acuity. Supposing it to be, as we have shewn reason to suspect, a result of increased nerve fibre excitability it must be due, just as peripheral reference is, either to an abnormal irritability or to an increased accessibility to stimulation.

Anatomical observations upon the results of nerve section and the processes of regeneration confirm the view that the restoration of the nerve is a process which is effected under considerable difficulties and is by no means so simple and inevitable as is perhaps sometimes supposed. It is probable that the fine axis cylinders which grow out from the central end of the nerve are much more numerous than the

axis cylinders originally present before the operation. Whether all this excess of new fibres is retained within the framework of the peripheral end of the nerve is open to question and it is possible that they grow down into the recovering area to some or perhaps to a considerable extent independently of the nerve trunk. If we are to suppose that a recovering area is thus invaded by a large excess of new axis cylinders, a plausible explanation will be available of many of the phenomena of recovery. A great increase in the possibilities of nerve fibre stimulation might for example under such circumstances be expected. Intensification would to a certain extent harmonise well with such an hypothesis. The intensification of a sensation can be estimated quantitatively to a certain extent. This can best be done with thermal sensibility by finding how large an area of normal skin it is necessary to stimulate with a given temperature in order to produce a sensation as intense as that produced by a standard cylinder at the same temperature. In this way it is found that the abnormal sensation is exactly reproduced by stimulation of normal skin, though it may be necessary to make the area stimulated in the latter case several hundred times larger than the abnormal area which yielded the intensified sensation. Such perfect reproduction of intensified sensation cannot be effected by heightening the stimulus applied to the normal, but is possible only by increasing the area stimulated. This observation seems to suggest that intensification means that the stimulus has acted upon a greater amount of nervous tissue than would a stimulus of the same size and strength in the normal. The persistence of intensification and peripheral reference would be accounted for by such an hypothesis, for it might be supposed that the recovering area was at first invaded by a great excess of axis cylinders, only a certain proportion of which could become connected with end organs and furnish the definitive sensibility of the part, while the other axis cylinders remaining unconnected with end organs would gradually atrophy and ultimately disappear, but would as long as any of them persisted endow the part with nerve fibre sensibility, and cause it to shew a slowly diminishing degree of intensification and peripheral reference. The increased accessibility to stimulation of the regenerating nerve trunk is another important phenomenon which would be very readily assimilated by this hypothesis.

Encouraging as is this interpretation of the facts we are not inclined to accept it as being complete. The special difficulty it presents is in regard to the elucidation of peripheral reference and intensification as they occur in response to minutely punctate stimuli as for example pain sensations elicited with a needle. It is very difficult to see how such a stimulus could be regarded as directly exciting such an excess of nervous tissue as would lead to sensations so exaggerated. If then we accept the hypothesis some supplementary mechanism other than that it assumes must be supposed to act. A very obvious suggestion is that during recovery there is an imperfect insulation of the nerve fibres from one another so that an impulse traversing one is communicated to those in its neighbourhood and the corresponding sensation thus magnified. The fact that myelination during regeneration is much slower than the formation of axis cylinders might be taken as confirming this supposition. We are not aware however of any histological evidence pointing to a delay in myelination so great as to correspond with the persistence of intensification and peripheral reference.

A consideration of certain pathological conditions in which irritative nerve lesions are present suggests that a persistent slight irritation of a sensory nerve may give rise to an increased excitability in consequence of which the response of the nerve to stimulation is excessive. The sensation aroused by stimulation of the irritable nerve is more intense and vivid than that aroused by similar stimulation of a normal nerve. The intensity of the response is independent of the sensory acuity of the given nerve, so that the latter may be hypoaesthetic and yet yield sensations of abnormal vividness. This is the condition usually found in cases of irritative nerve lesions. There is however no necessary relation between hypoaesthesia and excessive response. The irritation which causes the excessive response does not in itself affect sensory acuity which may be very low or practically normal. In the latter case the state of affairs is practically indistinguishable from a true hyperaesthesia for a stimulus which barely produces a faint sensation on the normal, produces on the abnormal a sensation of very much greater intensitiy.

In dealing with the question of whether a persistent tendency to irritation of the new fibres in a regenerating nerve area can be regarded as a more or less constant phenomen, it will be necessary to discuss and to attempt to bring into correlation many apparently disconnected facts.

In the consideration of the elementary physiology of the nervous system, a group of facts of fundamental significance has received less attention than its importance should perhaps have attracted. The facts to which we refer are those relating to the mechanisms whereby the nervous tissues are cut off from contact with the general substance of the body. The essential property of nervous protoplasm is its capacity on the one hand to respond to stimulation and on the other hand to yield stimuli. Primitively this capacity may be supposed to be absolutely generalised. In the nervous system as we know it, specialisation has advanced very far and the nervous tissues shew marked predilections to respond to certain stimuli and marked tendencies to react on certain tissues. Nevertheless there is reason to suppose that nervous protoplasm still possesses enough of its original generalised irritability to be affected by contact with tissues in which it is not normally in relation and to react upon such as an irritant. In other words although it has become specialised in such a way as to shew its full activity in response to special circumstances only, it cannot be regarded as ever being absolutely inert when it contact with foreign tissues. Such contacts may totally fail to arouse its specialised activities but they must therefore not be assumed to leave the nervous protoplasm totally unaffected. In other words supposing as the result of an injury a tract of nervous tissue is brought into relation with the connective tissues of the body complex reactions must occur at the point of contact, the tissues will irritate the nerves and the nerves will irritate the tissues. Possibily the irritation of the nerve will not be sufficiently intense to arouse its specialised activity but it will tend to give rise to a constant subminimal excitation. With regard to the effect upon the tissues, the nerve is of course incapable of exciting any of the customary response such as contraction, secretion and so forth, but it will act as an irritating foreign body and produce appropriate changes.

This series of phenomena is seen in its most striking form in connection with the large nerves of the limb which have been divided in an amputation. The out-

growth of new axis cylinders from the cut end produces a marked reaction of the connective tissues into which they grow. This reaction leads to the formation of a mass of fibrous tissue of remarkable density which surrounds and firmly encapsules the irritant which has led to its formation. The bulbous end of a divided nerve and the so called amputation neuroma are to be looked upon then as an expression of the irritating quality of nerve protoplasm and of the fact that this quality is constantly present and not due to the conduction of nervous impulses. At the same time it is clear that the new axis cylinders which are entangled in and encapsuled by the connective tissue of the bulbous end, do not find themselves in an indifferent medium for it is common knowledge that irritative nerve symptoms are very often produced and frequently develope into a serious and highly distressing complication. In such a case we are to suppose that the irritation is sufficiently intense to arouse the specialised activity of the nerve and cause spontaneous pain. In other cases the exaggerated tenderness of the bulbous ends shews that although the irritation is not intense enough by itself to excite actual nervous impulses it leads to the establishment of an irritability which causes the nerve fibres to yield exaggerated responses.

Clinical experience abundantly proves that the division of a sensory nerve is an interference with the equilibrium normally existing between nervous and connective tissues which carries with it the danger that in any given case prolonged or even permanent disturbance may ensue. Even when immediate suture of a nerve is performed a similar though less risk is incurred. Most clinicians of any experience must have seen cases in which, in spite of restoration of function having taken place to a considerable extent, the patient's life has been made a burden by the irritative symptoms which have developed.

That the insulation of nervous tissues from contact with others which are capable of irritating or being irritated by them is of great physiological importance is shewn by many facts in the structure of the nervous system and serves to explain certain anatomical features which are otherwise obscure. The elaborate investment of the cerebro-spinal axis in a series of specialised membranes and its isolation in a fluid of a highly specialised kind have generally been explained as mechanisms developed to protect the nervous structures from gross mechanical injury. When these arrangements are carefully considered the most striking character they possess, in addition to being protective in the ordinary sense, is the completeness with which they seclude the central nervous system from contact with the connective tissues of the body in general.

It is not necessary here for us to enter upon a detailed examination of the numerous anatomical facts bearing upon this matter. Before passing on however to those aspects of it which especially concern us, one other peculiarity of more general interest may be mentioned. It cannot be regarded as without physiological significance that in the structure of the central nervous system the ordinary connective issue of the body plays so very small and unimportant a part, while the skeletal properties which are peculiarly necessary in the brain and spinal cord are supplied by a special tissue closely related in origin with the actual nervous elements. It would seem that the neuroglial material owes its great development not merely, and perhaps even not chiefly, to its being mechanically successful

as a supporting tissue but also to its being, unlike all the mesoblastic tissues of the body, physiologically inert towards nerve protoplasm. The peripheral nerves from the very nature of their function cannot be protected from contacts which would produce reaction by a general seclusion such as is satisfactory in the case of the central nervous system. Each individual fibre therefore must be protected and restrained by a special envelope which need not be present around fibres contained in the central nervous system. The neurilemma seems to fulfil these requirements. It is absent or rudimentary in the brain and spinal cord where the nerve fibre can meet only such tissues as are physiologically inert, but it is present everywhere else. Provided with this sheath a nerve fibre can traverse any part of the body and remain inert to all the tissues with which it comes in contact except the end organ with which it is functionally related.

When a nerve trunk is divided and sutured, however carefully, there can be little doubt that the regenerating axis cylinders, which are more numerous than those of the normal nerve, cannot all of them reach and be contained within the neurilemma sheaths of the peripheral end. Some of them, probably even a large number, invade the tissues about the nerve trunk and meeting with material no longer physiologically inert tend to pass into a condition of abnormal irritability. Possibly, even supposing all the new axis cylinders could be conducted to the original neurilemma tubes of the peripheral end, they would still be subject to a certain irritation seeing that these sheaths undergo remarkable and well known changes after a nerve is cut. This neurilemma proliferation fills the sheath with a more or less cellular material through which the new fibre has to make its way. That this new tissue is as inert towards the axis cylinder as the normal nerve sheath seems doubtful, and the facts suggest that some time must elapse before physiological equilibrium is reestablished.

The above are the principal considerations which lead us to infer that an excessive irritability is aroused in nerve fibres which are undergoing regeneration. Certain further collateral evidence might be adduced in support of this conclusion but we do not propose to enter upon it here. We may however bring together one or two facts of a certain corroborative value in relation to the antagonism between nervous tissues and those of the body generally which we regard as of fundamental significance in physiology.

While the connective tissues act in such a way as to resist and restrain invasion by axis cylinder processes, these very antagonistic changes appear to exercise a stimulating effect upon the growth of the nerve substance. It is a familiar fact that an amputation neuroma contains a great length of convoluted and tortuous axis cylinders. The stimulus to this excessive growth and equally of course to the growth which accompanies regeneration has been generally assumed to come solely from the nerve cell of which the axis cylinder is a process. This supposition has left unexplained the striking fact that no regeneration occurs within the nervous system. It has been thought that the relative absence there of the neurilemma sheath is connected with this incapacity. The difficulty in enforcing this association seems to be that it cannot be shewn that the presence of a neurilemma sheath is essential to the sprouting of the cut axis cylinders which is the beginning of regeneration, for such sprouting occurs no less in an amputation stump than in a sutured

nerve. Supposing however the stimulus to regeneration be regarded as coming from the contact of the cut axis cylinders with extra-neural tissues, the absence of restoration after section of the cord would be explained while the significance of the presence of the neurilemma in one situation and not in the other would also be elucidated.

We have already touched upon some of the difficulties in making out the significance of the sensory end organs in the skin and have pointed out that no satisfactory generalisation has been made which brings their structure and distribution into relation with the sensory acuity of the skin. We do not propose to enter upon any further extended discussion of this very complicated matter here but would call attention to certain very obvious facts in the structure of these end organs. In the great majority of all their numerous forms, the encapsulation of the organ in a more or less structureless sheath of considerable thickness is a well marked feature. Contained within this sheath is a naked nerve filament which is usually much convoluted. The frequency of this arrangement suggests that the protection of the bare nerve fibre from contact with tissues not physiologically indifferent to it is an important part of the function of the end organ. It is generally accepted that these encapsuled organs are concerned with sensations other than those of pain, while fibres which end in free ramification swithout encapsulation are regarded as having to do with pain sensations. If this distinction could be accepted as a fact some light might possibly be thrown upon the nature of pain sensibility, the naked ramifications of the pain fibres being regarded as kept in a condition of excitability slightly in excess of the other nerve terminations, and pain being looked upon as a sensation normally "intensified"[1]).

The physiology of sensibility to pain presents many extremely difficult problems especially in regard to the nature of the peripheral mechanism. In the other forms of sensibility the nervous impulse which arouses the sensation is initiated by a single simple physical process whereas in the case of pain the nervous impulse may be aroused by any one of a number of heterogeneous processes of thermal, chemical, mechanical or electrical nature. The common feature presented by these is that they are capable of damaging the tissues to which they are applied. Little if any light however is thrown upon the intimate nature of the stimulus by this fact seeing

[1]) From the foregoing and what we have said earlier it will be seen that two suggestions are put forward as to the significance of the sensory end organs of the skin, one being that they are concerned with the localisation of sensation and the other that they serve to insulate the terminal nerve twigs from contact with the non-neural tissues of the body. The two views are at first sight incompatible with one another for if the naked nerve ramifications are the terminal structures concerned with pain sensations and get their special capacity from the absence of encapsulation according to the second suggestion, it would follow according to the first suggestion that pain sensations are not localisable. The difficulty is a serious one; certain considerations however suggest themselves as possibily rendering it not altogether insurmountable. In the first place opportunities for testing the localisation of sensations of mere pain unmixed with any other sensation are not such as to allow any very positive statement to be made as to the normal extent of this capacity; secondly sensations of pain being habitually accompanied by an almost immediate motor response the localisation of them is aided by this accessory mechanism; finally in parts of the body (serous cavities) where pain is the only form of sensibility, pain when experienced (e. g. in disease) is characteristically vague and diffuse however intense it may be.

that the characteristic sensation is almost always produced by a strength of stimulus of such a low grade that any actual injury can scarcely be conceived to have been inflicted. Moreover experience in testing sensibility to pain shews that a very little actual injury inflicted upon a pain spot destroys its sensitiveness. We must suppose therefore that in all ordinary testing with stimuli of about the normal threshold strength no more real damage is done to the tissues than in testing any other form of sensibility. Thus the characteristic feature of pain sensibility is so to say the *disproportion* between the stimulus and the response, for the function to be served is the anticipation of injury rather than the notification of it. It is difficult to see how a requirement such as this and differing so much from the conditions necessary for other forms of sensibility, could be satisfied unless the nervous tissue concerned is in a state of especially heightened excitability. That heightened excitability can be established and that it leads to the very disproportion between stimulus and response which seems to be demanded for the normal mechanism of pain sensibility, is abundantly proved by the facts of intensification in a recovering area. The suggestion that the essential mechanism in pain sensibility is the permanent excessive excitability of the nerve filaments which subserve it, is possibly to some extent borne out by the well known instability of this form of sensibility and the fact that it is liable to disorder to a far greater extent than any other. In considering the views which are expressed here it will naturally be asked whether there is any direct evidence that the peripheral pain mechanism is more readily excitable than the other mechanisms. As it happens this question has already been dealt with from another aspect by *von Frey*. In his classical researches upon the sensibility of the skin he shewed that since touch spots and pain spots could be excited by similar stimuli, their thresholds could be compared. He found that when a mechanical stimulus was used the pressure needed to excite pain sensations from the pain spots was higher than that needed to excite touch sensations from the touch spots. That is to say the threshold for pain is higher than that for touch, a result which might be expected from a consideration of general principles. With punctate stimulation with the faradic current he found however a striking difference in that the pain threshold was lower than the touch threshold. Moreover he found evidence strongly suggesting that with this form of stimulus it was the terminal nerve fibre rather than the end organ that received the stimulation and originated the response. These observations seem to shew that faradic stimulation furnishes a means of comparing directly the excitability of two groups of nerve fibres, for it allows the influence of the end organ to be excluded. Tested in this way then the pain nerve fibres are found to be more readily excitable than the touch nerve fibres. Thus these observations of *von Frey* furnish direct evidence of the excess of excitability which we have given other reasons for supposing to be a normal feature of the pain mechanism and possibly an explanation of some of its perplexing characteristics.

In attempting to shew the importance of the reactions which arise when nervous tissue is brought into direct contact with the extraneural connective tissues of the body we have spoken as if such disturbances of what may be called neurosomatic equilibrium were always of traumatic origin. That such conditions may arise apart from injury is shewn in the various forms of connective tissue over-

growth of neural origin which when multiple and wide spread are referred to as *Recklinghausen's* disease or diffuse neuro-fibromatosis. Such conditions shew the manifestations which may be expected to ensue when there is a breach in the isolation of nerve fibres from the other tissues; namely connective tissue overgrowth on the one hand and increased irritability of the affected nerves on the other.

The foregoing discussion has been almost necessarily somewhat diffuse and it is therefore desirable that we should resume in summary form the principal considerations put forward in it.

Normal sensory nerves when stimulated in the part of their course proximal to their areas of distribution yield corresponding sensations when subjected to certain specific stimuli especially cold and the faradic current (specific excitability of nerve fibres). The fact that they do not respond unmistakeably to all the primary stimuli is probably due not so much to insusceptibility as to inaccessibility to stimulation.

The sensations aroused by nerve fibre stimulation are of normal characters except in regard to localisation. They are felt not at the point stimulated but in the area of distribution of the nerve — in the peripheral part of the area if the stimulus is moderate, throughout the area if the stimulus is energetic.

During regeneration of a sensory nerve the regenerating part shews a great increase in the specific excitability of its fibres. The primary stimuli (touch, pain, heat, cold and the faradic current) readily arouse corresponding sensations.

The sensations aroused by nerve fibre stimulation of regenerating nerves are of characteristic quality corresponding with the stimulus and have precisely the same peculiarities of localisation as have sensations due to nerve fibre stimulation of normal nerves.

Peripheral reference in the recovering area itself at an early stage reproduces all the characters of nerve fibre stimulation as regards localisation, viz absence of sensation at the spot stimulated, localisation of sensation to the periphery of the area if the stimulus is moderate, and diffusion of the sensation throughout the area if the stimulus is energetic.

It is therefore highly probable that peripheral reference is due to nerve fibre stimulation and that in the recovering area the regenerating nerve fibres are abnormally accessible to stimulation.

It is suggested that the restoration of true local sensibility may be due to the re-establishment of the connection between nerve fibre and end organ.

In view of the fact that the reappearance of true local sensibility does not abolish reference, and the fact that the latter persists for a very long period and disappears gradually it is suggested that in the recovering area there is an excess of new axis cylinders over the number normal to the part. This view is held to be confirmed by the histological facts of regeneration.

Intensification of sensation in the recovering area is characteristic of all sensations whether they are elicited by a threshold stimulus above, at or below the normal.

It is therefore concluded that intensification is a phenomenon altogether distinct from and independent of sensory acuity.

Pathological evidence tends to shew that excessive reponse to stimuli is an indication of persistent slight irritation of the nerve. It is therefore suggested that the intensification of sensation elicited from the recovering area is due to the regenerating nerve fibres being subject to chronic irritation.

The source of this irritation is found in the contact of the new nervous tissue with the non-nervous tissues of the part and the consequent reactions set up.

It is pointed out that the insulation of nervous tissue from non-nervous is very elaborately provided for in the anatomy of the normal nervous system and is probably therfore of essential importance. The neurilemma and the end organ of the peripheral sensory nerve are regarded as having important insulatory functions. It is suggested that if the free terminal ramifications of sensory nerves are the end organs subserving pain sensibility, the specific quality of the sensations resulting from stimulation of them may be due to a slight normal irritation consequent on incomplete insulation. The suggestion is strengthened by the observation of *von Frey* that for faradic stimulation the pain threshold of the skin is lower than the touch threshold.

In conclusion we may add that the general purpose of this paper is an attempt to shew that the peculiarities of function displayed by a cutaneous area during the recovery of sensibility, strange in many ways as they are, are not altogether isolated phenomena but can be brought into correlation with many well known facts in the anatomy and physiology of the nervous system and in its modes of reaction to injury and disease.

**Description of Figures.**

Figs. 1 to 4. Recovery in area of Left Saphenous nerve. The nerve was divided at the level of the knee joint. The illustrations embody the results of detailed examination 11 months after the operation.

In each case the *broken outline* is the outermost limit of change of any kind which followed the nerve section, and the *continuous line* shews the area anaesthetic to touches with cotton wool or the camel's hair brush at the time of examination.

Fig. 1. **Sensibilty to touch,** tested with *von Frey* hairs.

*Dots.* Touch spots which reacted to hair of 70 mgr pressure (normal threshold).

*Steres.* Touch spots which reacted to hair of 140 mgr pressure.

*Crones.* Touch spots which reacted to hair of 800 mgr pressure.

*Circles.* Touch spots which reacted to hair of 3480 mgr. Peripheral Reference not indicated.

Fig. 2. **Sensibility to pain,** tested with authors' algometer at pressure of 2240 mgr. The dotted area is that within which the phenomena of Intensification and Peripheral Reference were obtained. All the referred sensations were felt within the lower end of the area enclosed by the continous line.

Fig. 3. **Sensibility to heat.** The dots indicate the places which yielded the sensation hot when touched with a copper cylinder with a contact surface 1 mm in diameter at a temperature of 50° C.

Fig. 4. **Sensibility to cold.** The spots marked are those which yielded the sensation cold when touched with a copper cylinder with a contact surface 1 mm in diameter at a temperature 0° C.

*Dots* indicate places which yielded sensations of cold felt locally.

*Crones* indicate places which yielded sensations of cold felt peripherally.

*Circles* indicate places which yielded sensations of cold felt locally and peripherally.

Figs. 5 and 6. Middle Cutaneous nerve of Right Thigh.

**Sensibility to cold.** The spots marked are those which yielded the sensation cold when touched with a copper cylinder with a contact surface 1 mm in diameter at a temperature of 0° C.

*Dots* indicate places which yielded sensations of cold felt locally.

*Crones* indicate places which yielded sensations of cold felt peripherally.

*Circles* indicate places which yielded sensations of cold felt locally and peripherally.

Fig. 5. $3^1/_2$ months after section of nerve shewing the condition immediately before the beginning of recovery. The fringe of normal cold spots has been marked out immediately around the area of thermoanaesthesia.

Fig. 6. 6 months after section of nerve. Recovery of sensibility to cold well marked.

Fig. 7. The Distribution of proximal and peripheral reference. Internal cutanueou of left forearm. Recovery well advanced. Area tested with cylinders at a temperature of 0° C. Each area indicates a spot the stimulation of which yielded a referred sensation of cold. The direction of the arrow indicates the direction of the reference. Double arrows mark spots which yielded peripheral and proximal reference. The lines shew the position of the incisions through which the three branches of the nerve were divided.

Fig. 1

Fig. 2.

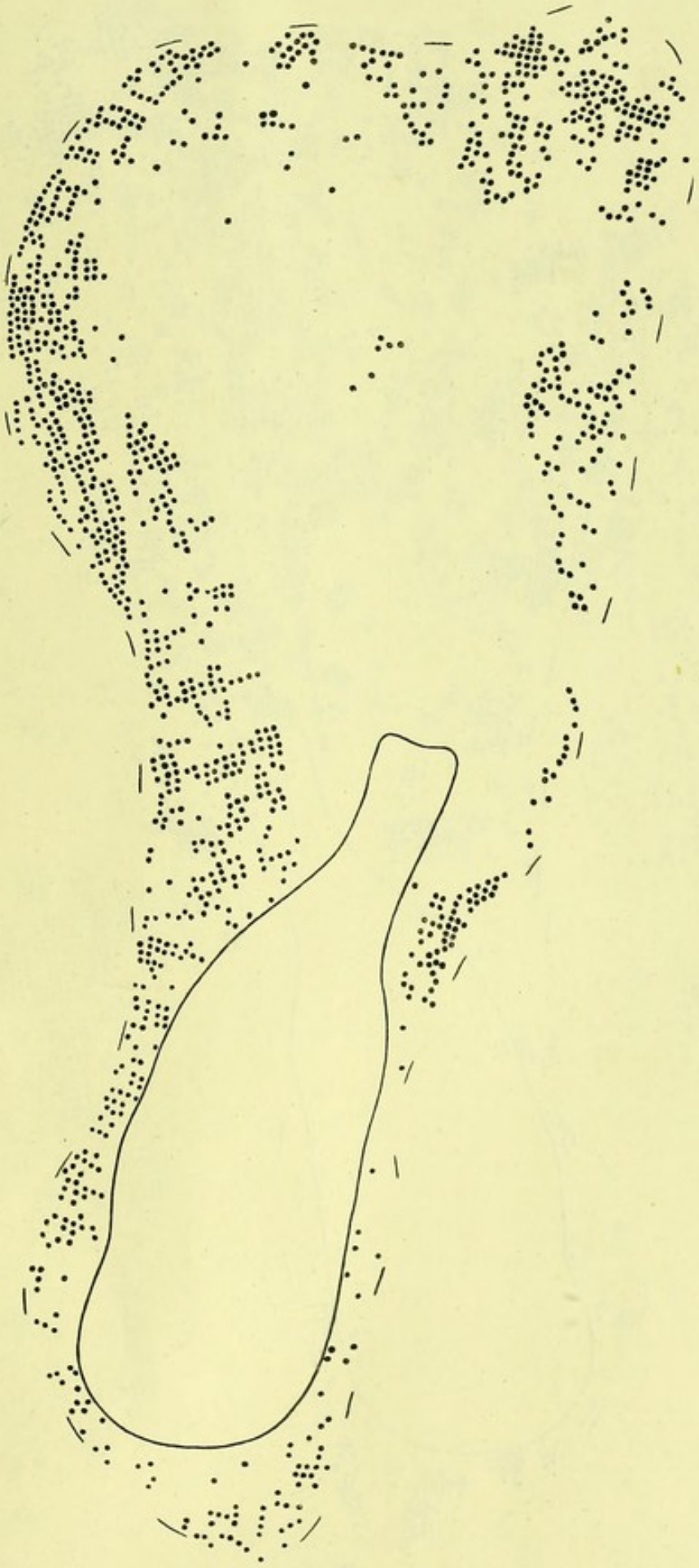

Fig. 3.

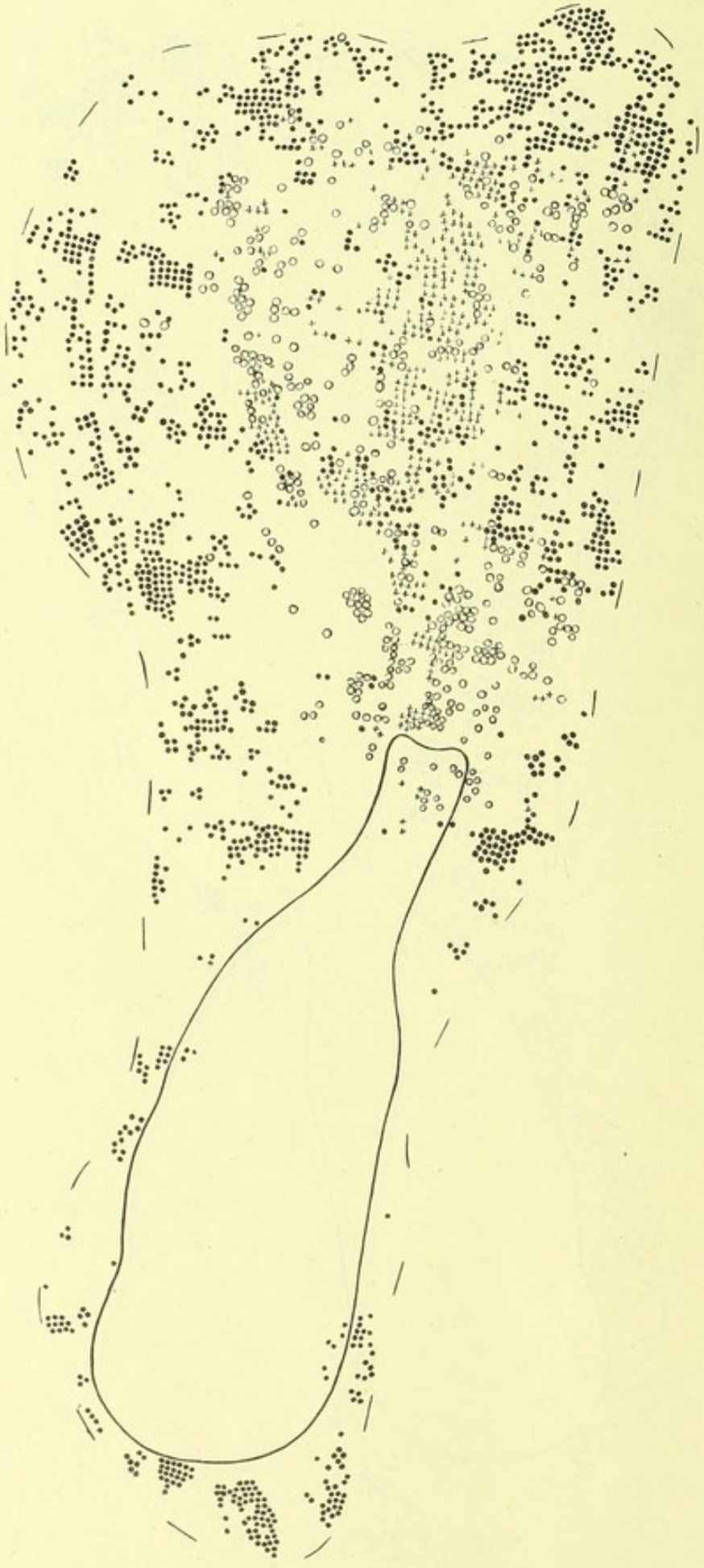

Fig 4.

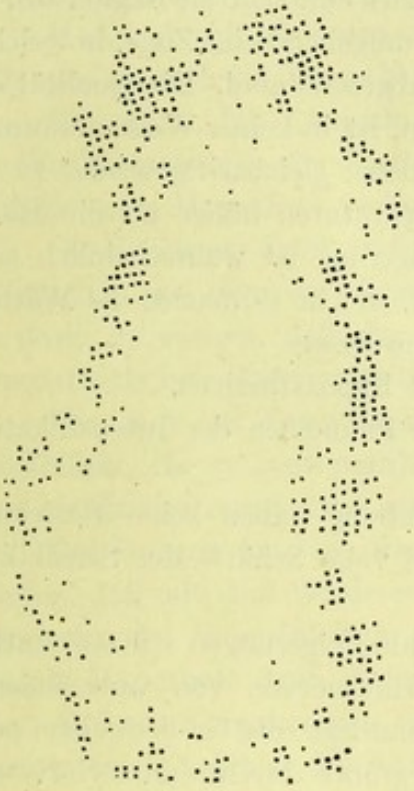

Fig. 5.

Fig. 6.

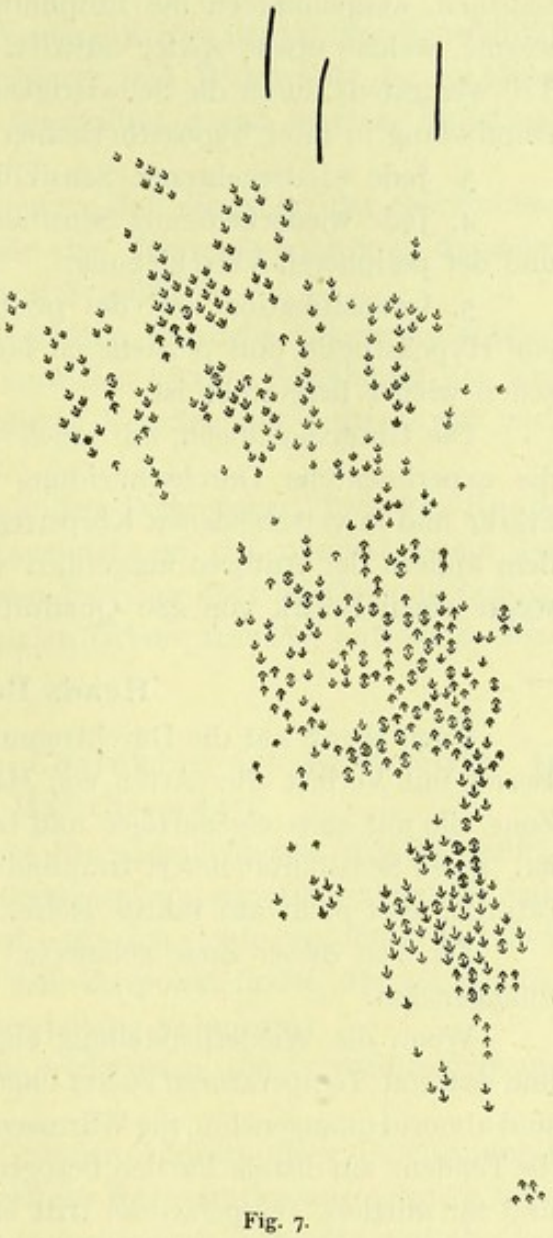

Fig. 7.

**Resumé.**[1])

1. Unmittelbar, bevor sich die ersten Anzeichen der Wiederherstellung zeigen, weist ein seiner Nervenversorgung beraubter Hautbezirk eine zentrale Region auf, wo alle Arten der Hautsensibilität verloren sind und sie umgebend eine Zone, in welcher alle Arten der Hautsensibilität in ihrer Schärfe herabgesetzt sind. Die Qualität der Empfindungen, die da hervorgerufen werden können, ist in keiner Weise abnormal.

2. Alle Arten der Sensibilität haben die Tendenz, gleichzeitig wieder zu erscheinen, ausgenommen die Empfindung für Temperaturen höher als die Hautwärme, welche etwas später auftritt. Diese Verzögerung ist wahrscheinlich zum Teil wenigstens durch die Schwierigkeit zu erklären, welche es macht, die Wärmeempfindung in ihrer hypoästhetischen Form nachzuweisen.

3. Jede wiederkehrende Sensibilität ist zuerst hypoästhetisch.

4. Jede wiederkehrende Sensibilität zeigt das Phänomen der Intensifikation und der peripheren Verschiebung.

5. Intensifikation und die periphere Verschiebung haben keine Beziehung zur Hypoästhesie und persistieren lange, wenn die volle Schärfe der Sensibilität schon wieder hergestellt ist.

Die Untersuchungen, auf welche sich diese Schlußfolgerungen stützen, hatten die experimentelle Durchschneidung von sieben Hautnerven von verschiedener Stärke und in verschiedenen Körperregionen zur Grundlage, die bei dem einen oder dem andern der Autoren ausgeführt wurden. Der größte durchtrennte Nerv versorgte einen Bezirk von 280 Quadratzentimetern.

## Heads Beobachtungen.

Nach Head hat die Durchtrennung eines Nerven zur Folge, daß ein zentraler Bezirk mit Verlust aller Arten von Hautsensibilität auftritt — umgeben von einer Zone, die mit einer eigenartigen und besonderen Form von Sensibilität ausgestattet ist. Diese Sensibilität liefert Empfindungen auf Schmerzreize, auf extreme Temperaturen, aber nicht auf taktile Reize.

Die von dieser Zone gelieferten Schmerzempfindungen sind ganz besonders unangenehm.

Wenn die Wiederherstellung eintritt, erscheint die Sensibilität für Schmerz und extreme Temperaturen zuerst ohne Tastsensibilität. Die Schmerzempfindungen sind abnorm unangenehm, die Wärmeempfindungen abnorm intensiv und beide haben die Tendenz auf distale Partien bezogen zu werden. Die Sensibilität für Berührungen und für mittlere Temperaturen tritt erst später wieder auf.

Gleichzeitig mit ihrem Auftreten verschwindet die Intensifikation von Schmerz und Temperaturempfindungen und die distale Verschiebung. Diese Phänomene werden durch die Hypothese erklärt, daß es zwei verschiedene Arten von Nervenfasern gibt, von denen die eine der Empfindung für Schmerz und extreme Temperaturen (protopathische) dient und zu einem früheren Zeitpunkt regeneriert, und eine andere, welche die Sensibilität für Berührung und mittlere Temperaturen trägt und erst später regeneriert (epikritische).

[1]) This resumè is an abstract of the paper actually read at the Congress & therefore includos no summary of the chapter here published which deals with the physiological interpretation of Intensification & Peripheral Reference.

Die Beobachtungen, auf welche Heads Schlüsse aufgebaut sind, wurden nur an einem einzigen Hautbezirk von fehlender Sensibilität gemacht, der experimentell auf der Haut des Vorderarms erzeugt war.

Heads Arbeit wird also sowohl bezüglich des von ihm gegebenen tatsächlichen Befundes als auch der daraus abgeleiteten Schlußfolgerung einer Revision unterzogen.

Wir zeigen, daß in keinem von unseren wiederholten Versuchen die Verzögerung im Wiedererscheinen der Tastempfindung zu finden war, welche Head beschreibt und die seine Hypothese verlangt.

Die Erklärung dafür, daß er nicht das Wiederauftreten der taktilen Sensibilität gleichzeitig mit dem der Sensibilität für Schmerz und Wärmereize beobachtete, ist darin zu suchen, daß die erstgenannte Sensibilität zuerst in einer auffallend hypoästhetischen Form auftritt.

Man muß der Tatsache Beachtung schenken, daß die Abart der thermischen Sensibilität, die er protopathische nennt, nur eine Thermohypoästhesie darstellt, eher als eine getrennte und spezifische Art von Sensibilität.

Bei keinem der von den Autoren angestellten Versuche konnte konstatiert werden, daß mit dem Wiedererscheinen der normalen taktilen Sensibilität das Verschwinden der Intensifikation und der peripheren Verschiebung auftrat, was nach Heads Hypothese dann platzgreifen mußte.

Außerdem ergaben sich noch zahlreiche andere Diskrepanzen zwischen Heads Resultaten und denen der Autoren. Es ist anzunehmen, daß mindestens ein Teil davon durch die begrenzten Möglichkeiten von Revision oder Bestätigung bedingt sind, die Head bei seinem einem Experiment zu Gebote standen, auf das er seine Untersuchungen beschränkte.

## Betrachtungen über den speziellen Charakter der Sensibilität in regenerierenden Hautbezirken.

Es kann gezeigt werden, daß bestimmte Eigentümlichkeiten der Sensibilität zum erstenmal dann auftreten, wenn die Wiederherstellung einsetzt und daß sie ganz spezifisch für den Prozeß der Regeneration sind — da sich nichts, was ihnen irgendwie gleichen würde, in dem affizierten Bezirk in dem Zeitpunkt findet, der unmittelbar den ersten Anzeichen der Funktionswiederherstellung vorangeht.

Von diesen Eigentümlichkeiten sind die wichtigsten, die Intensifikation und die periphere Verschiebung.

Deshalb und aus gewissen anderen Gründen können diese Erscheinungen nicht als Stadien in dem fortschreitenden Prozeß der Regeneration angesehen werden, sondern sie müssen als dazutretende Erscheinungen aufgefaßt werden und als akzidentelle, was die tatsächliche Wiederherstellung der Funktion angeht.

Es ist wahrscheinlich zu machen, daß sie im Wesen beruhen und zusammenhängen mit einem Zustand abnormaler Irritabilität der regenerierenden Nervenfasern. Es wird gezeigt, daß wahrscheinlich ein konstanter leichter Reizzustand der Nervenfasern dazu tendiert, eine übertriebene Reaktion auf einen wirksamen Reiz zu verursachen, aber nicht notwendig eine vermehrte Reizbarkeit oder eine wirkliche Hyperästhesie.

Dieser Standpunkt stimmt überein mit dem bekannten Fehlen einer Beziehung zwischen sensorischer Schärfe und der diskutierten Erscheinung.

Unter Intensifikation wird jene Eigenschaft wieder erwachender Sensibilität verstanden, auf Reiz eine abnorm intensive Antwort zu geben, z. B. so daß Schmerzempfindungen ungewöhnlich unangenehm, kalte Empfindungen übertrieben lebhaft sind.

Unter peripherer Verschiebung ist die Tendenz aller von einem regenerierenden Bezirk aus erregten Empfindungen zu verstehen, in dessen distalen Partien empfunden zu werden — entweder allein wie in den ersten Stadien oder zusammen mit einer Empfindung an dem Ort des Reizes.

Diese Phänomene ändern sich nicht gleichermaßen mit der Schärfe der Sensibilität. Sie können Empfindungen begleiten, die von einem noch ausgesprochen hypoästhetischen Bezirk aus ausgelöst werden oder von einem Bezirk mit normaler Schärfe der Sensibilität.