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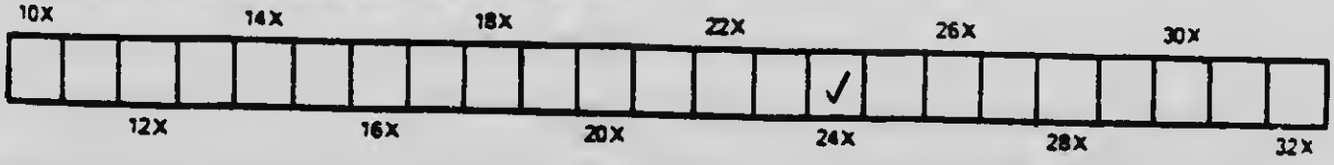

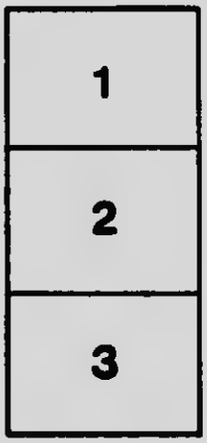

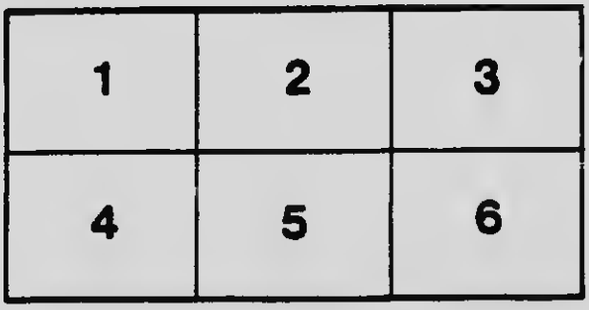

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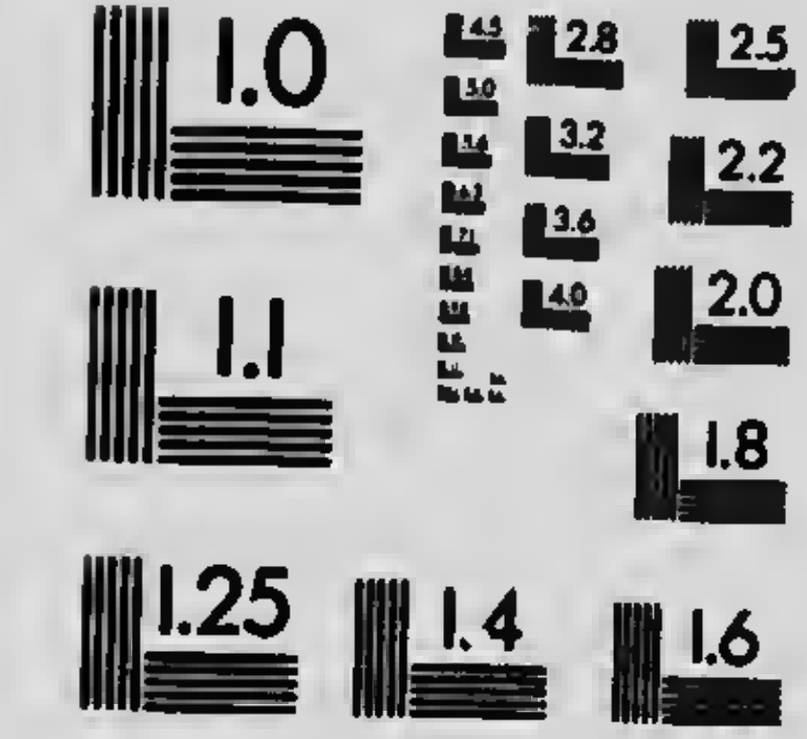

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SOME PHYSIOLOGICAL ASPECTS OF REFERRED PAIN

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PAIN has been defined as a variety of sensation whose existence we desire to terminate; it is a variety of sensation in that it requires the same physiological conditions as does sensation; namely, a nerve and nerve-centre and the presence of consciousness.

Thus, in leprosy, where the nerves are degenerated, there is no pain in the parts affected, and in paraplegia from complete transection of the spinal cord, there is no pain in the legs. When the nerve-centre is itself narcotized, pain is abolished; in the former cases analgesia is due to a peripheral, in the latter to a central, cause. There are, then, both physical and mental factors in pain. "Christian Science" has lost the sense of the proportion between these and magnifies the latter to the exclusion of the former.

We might classify the varieties of pain as follows:—(1) Pains from an over-stimulated sense-organ as, for instance, from too bright a light, a rasping sound or discordant intervals, excessive heat or cold, muscular cramp. (2) Pains from injury, mechanical or otherwise, to an exposed or naked nerve fibre; as from a thorn or a corn in the skin, a foreign body in the tooth-pulp, pressure of pus in a boil or abscess, or of blood within rigid capsules, the freezing of a nerve; and all cases of injury to nerves, such as transfixing or crushing them. Thus, Romberg's saying that "pain is the prayer of a nerve for blood" is not universally true, for a nerve may be painful from being engorged with blood. (3) Pure pains or pains of viscera and of such organs as are not provided with nerves of touch proper, besides the viscera themselves, the blood-vessels, the meninges, the periosteum, and the nerves themselves. (4) Pains called "referred" and sometimes "sympathetic" and "reflex." (5) Hallucinatory pains of "the absent member."

The viscera, in which we may include the heart, the blood-vessels, and nerves, are apparently so badly supplied with nerves

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of touch, that we are normally unaware of their presence and cannot, therefore, localize them except in the vaguest manner. Though we must believe that afferent currents are at all times ascending from the viscera, they do not in a state of health obtrude themselves on our consciousness. This is well exemplified in the case of the lungs from which it has been definitely proved afferent currents are continually ascending by the vagi to the respiratory centre, although these currents certainly do not enter into consciousness. Similarly, the iris, the pleura, the heart, the liver, and gall-bladder, the reproductive viscera, the periosteum, and the meninges, provided they are perfectly normal, are entirely outside the mental realm. The last mentioned tissues—the spinal meninges—are interesting in this connexion, seeing that the existence of recurrent sensibility as an exception to the Bell-Magendie Law is to be explained by the presence of fibres afferent from the coverings of the spinal cord. It will be remembered that it is their stimulation in the peripheral stump of the anterior root which gives rise to the pain occasionally experienced in experimental irritation to some of those roots. Surgeons tell us that the normal liver is insensitive to diagnostic puncture, and the cerebrum itself to operative procedure.

But this state of things is considerably altered when the viscera become abnormal—inflamed, congested, catarrhal, ulcerated, or distended. Here the pain may arise either from morbid mucosæ or from morbid muscles, for instance in cramp; or from both together. The pains of iritis, angina pectoris, aneurysm, pericarditis, pleurisy, bronchitis, gastritis, gastric and intestinal colic, the pain of colitis, of biliary and renal colic, in diseases of the bladder, testes, ovaries, and uterus, are therefore true visceral pains or cases of pure algesia. In certain forms of neuritis, for instance in sciatica, the congestion or tension in the perineural sheaths irritating the nervi nervorum must be the basis of the pain; the nervi nervorum are, therefore, purely algesic nerves. It is, of course, theoretically possible that there are no nerves of pure pain in the viscera, and that the nerves of common sensibility are stimulated only by such excessive irritations as become painful in consciousness, whereas the normal states of the tissues constitute only subliminal stimuli. Physiologists have, however, a good deal of reason to hold that there are nerves, other than visceral afferents, which are nerves of pure pain. In physiological language, then, the viscera and other autonomic structures (Langley) possess afferent fibres which in health are stimulated so slightly that localization is extremely vague or non-existent, whereas in morbid conditions these fibres convey impulses

which are decidedly painful, although they may not lead to any more definite localization.

It is these visceral pains that have a great tendency to be referred into the skin. In order to understand how this can take place, we must have before us the physiological anatomy of a spinal cord segment and its connexion with the autonomic system.

The visceral (autonomic) afferent neurone, leaving some peripheral tissue, passes through one of the prevertebral ganglia and enters the vertebral chain of the sympathetic system. In this it travels headward and turns aside into a white ramus communicans, whence it enters the spinal nerve immediately after its formation and thence turns back into the posterior root of that nerve. In the ganglion of this root it has its trophic cell after the manner of the much better known afferent somatic fibres. Passing central of the ganglion, it enters the dorso-lateral region of the white matter of the cord in which it bifurcates, an ascending limb travelling, presumably, towards some cerebral region, the descending limb entering the grey matter of the posterior horn in which it and its collaterals may terminate synaptically.

Now it is clear that the afferent neurone from the skin (sensory cutaneous fibre) and the afferent neurone from the viscus have a common path of entry into the cord from the posterior root inwards; the theory of referred pain (tenderness or sensation) is that somewhere in this common path the excitement of the splanchnic afferents is transferred to the somatic afferents, and that, the cerebral centre for these being stimulated, the mind suffers an illusion and refers the source of the irritation out to an area of skin. Psychologically, this is an algesic illusion due to peripheral reference. All viscera whose afferent fibres enter white rami communicantes, or their homologues, may therefore have skin-areas to correspond with them; or, put otherwise, in all such spinal segments whose nerves receive white rami communicantes, there is the possibility of the transference of nerve-impulses from visceral to somatic afferent neurones.

As far as we know, visceral irritation does not give rise to referred pain in muscles, although the afferent fibres from muscles also enter by the posterior roots. As far as we know, cutaneous irritation does not give rise to referred pain in viscera; so that it has been said, the skin is sympathetic with the viscera, but not the viscera with the skin. The most likely place of the transference is in the grey matter of the spinal cord, for here the naked collaterals of the autonomic and the somatic afferent fibres are in close contiguity; it is a much more probable place than is the posterior root

in which both fibres are still medullated. The seat of transference of irritation (nerve-impulses) is, therefore, more probably in cord segment than in posterior root; we shall later see that this view is pretty fully corroborated.

We might now look a little more in detail at some of the evidence which Professor Langley has brought forward to indicate the existence and the precise path of entry of the afferent fibres of the autonomic system. In the first place, they do not enter the cord by the anterior roots because stimulation of the central end of the cut anterior root gives rise to no reflex actions (Bell-Magendie Law). They do not enter by the grey rami communicantes, because stimulation of the central end of a cut grey ramus calls forth no reflex actions. From other data we know that the grey rami contain only efferent fibres (the somatic vaso-motors).

We have, therefore, only left as paths of entry the white rami and the posterior roots. First of all, stimulation of the central end of a cut, white ramus does give rise to reflex action, proving that the white ramus contains afferent fibres. This is confirmed by the following observation: a section of the spinal nerve inside the vertebral canal but, of course, peripheral of the posterior ganglion, causes all the medullated fibres of the white ramus to degenerate, therefore, all the afferent fibres in the white ramus must have their trophic cells central of this spot, and as there are no afferent fibres in the anterior roots, the trophic cells must be found in the posterior ganglion. Conversely, if the splanchnic nerves are cut or the sympathetic chain itself, no degenerated fibres are found in any of the white rami, showing that the cells trophic for these fibres are situated somewhere proximal of the place of entrance of these fibres into the nerve-roots.

But further, if one considers the path of entry of the afferent fibres from the skin, it will be obvious that these must have their trophic cells in the posterior root ganglia, for the cutaneous sensory fibres have no peripheral ganglia to pass through en route for the spinal cord.

The same lines of reasoning apply to those structures homologous with the white rami; namely, the origins of the pelvic splanchnics or sacral autonomic fibres. If the posterior roots of the second, third, and fourth sacral nerves be cut outside the ganglia, one-third of all the fibres in the pelvic splanchnics are found to be degenerated, proving such fibres to be afferent. Once again, when the English worker, Warrington, cut both roots of the first thoracic nerve (the posterior between the cord and the ganglion),

and found that one hundred and thirty-six fibres in the white ramus did *not* degenerate, he demonstrated that these still normal fibres entered by the posterior root, in which they had trophic cells, for it had been previously shown that not all the fibres in the white rami are efferent, and that no fibres of white rami enter the cord by the anterior roots. Only those skin-areas with afferent neurones which enter the grey matter of the cord along with visceral fibres through white rami or such homologues as the pelvic splanchnics, can have referred pain by transference of nerve-energy in their own cord-segments. Thus, the segments receiving fibres from that part of the sympathetic system known as the dorsal outflow (from second dorsal to second lumbar nerves, inclusive) can be the seat of such direct transference as leads to referred pain, as well as segments corresponding to the second, third, and fourth sacral nerves which are similarly related to the sacral autonomic outflow.

Since, then, the fifth to the eighth cervical nerves and the first dorsal nerve have no white rami communicantes, the segments to which they are related are not the seats of the transference necessary to evoke referred pain, and hence the related skin-areas are exempt from it and constitute what Dr. Head has called "the brachial gap." Although, indeed, the first to the fourth cervical nerves have no white rami, yet since the segments of their origin are accessible to the transference of nerve-impulses from irritation in the medulla, the skin innervated by these nerves is liable to referred pain, which we might describe as due to medullary irradiation. According to Dr. Head there is also a lumbar gap related to the third and fourth lumbar segments.

We might now take some definite examples of referred pain well known to medical diagnosticians. The referred pains of dyspepsia, gastric ulcer, and hepatic disease are experienced in the cutaneous distributions of the anterior and posterior branches of the fourth and fifth dorsal nerves, because, as Dr. James Ross pointed out in *Brain*, as long ago as 1887, the afferent splanchnic fibres from the stomach and liver enter into the fourth and fifth dorsal segments. In lesions of the small intestine, the pain is referred chiefly to the anterior division of the ninth, tenth, and eleventh dorsal nerves, that is around the umbilicus. In diseases of the kidney and ureter the pain is in the skin-areas related to the tenth and eleventh dorsal and the first and second lumbar segments, and therefore related to the distribution of the ileo-inguinal and genito-crural nerves. Morbid states of the ovaries cause referred pain in the areas of distribution of the posterior branches of the second lumbar nerves and of the

anterior and lateral branches of the first, second, and third lumbar nerves:

Similarly, pain referred from the testicle involves the first lumbar segment, that is, the ileo-inguinal nerve. Pains from lesions of the bladder and prostate in the male are experienced in skin-areas related to the third and fourth sacral segment, and as these receive the pudic nerve, the reference is to the tip of the penis. The rectum causes pain to be referred to the distribution of the second and third sacral segments, that is, to the areas innervated by the small sciatic nerve. The uterus gives pain referred to the nerves at the back of the sacrum from the involvement of the second, third, and fourth sacral segments.

We must, therefore, believe, in cases of referred pain, that there is somewhere in the grey matter of the cord or medulla an actual transference of neurine from a deep afferent fibre to a superficial one. If this neurine were to be transferred from the terminations of the autonomic afferent fibre to the cells of origin of any efferent neurone, we should have reflex action instead of referred pain. But, as a matter of fact, it is possible to have both simultaneously, as in cases of severe referred pain over certain intercostal spaces being associated with actual spasm of the underlying intercostal muscles. The presence of true reflex action along with the severe referred pain of hemicrania is well illustrated by the following case which lately came under my notice. A patient had severe, periodic, hemicranial headache, associated with vaso-constriction on the same side of the head, secretion from the nasal glands, spasm of the sterno-mastoid, and vomiting. The interpretation of this complex of symptoms is probably as follows: the irritation due to the gastric catarrh and toxæmia violently stimulated certain terminals of the afferent gastric branches of the vagus, which conveyed nerve-impulses towards the sensory centres of the ninth and tenth nerves in the medulla oblongata. Here there was transference of irritation to certain terminations of afferent neurones of the ophthalmic division of the fifth nerve, giving the severe post-orbital headache, but there was also irradiation of impulses to the following centres—vaso-motor, vomiting, for the spinal accessory nerve, and for the glands of Bowman, producing, respectively, vaso-constriction of the vessels on the side of the face, vomiting, spasm of the sterno-mastoid, and the artificial coryza.

There must have been, in this case, a very wide irradiation of impulses from the sensory centre of the vagus to neighbouring centres of the medulla oblongata: in this way we can understand

how it is that very great pain can produce shock, if by "shock" we understand what some assert it to be, over-stimulation of the vaso-motor centre resulting in general vaso-motor constriction. (On the view of others it is rather a reflex inhibition of the vaso-motor centre.) The irritation produced by lesions in some structures, small in themselves, is very liable to be referred to areas of skin of considerable size, that is to *irradiate*. Thus, in dental caries, the transference is from some of the inferior maxillary neurones to others of the same branch of the fifth nerve, giving the face-ache so characteristic of tooth-ache. But, of course, the transference may be to another branch of the tri-facial nerve, as in a case I noticed lately, in which unilateral nasal turgescence produced considerable pain in the normal maxillary antrum of the same side, that is, the transference was from neurones of the ophthalmic branch to the superior maxillary branch of the fifth nerve.

As every one knows, a large number of headaches are pains referred from regions other than cephalic. The headache of gastric and hepatic catarrh is probably a reflex pain, resulting from severe vagal irritation, the transference being from the medullary terminations of the vagus to certain afferent neurones of the tri-facial. That the vagus is in this case the afferent path from the stomach to the central nervous system, is rendered the more probable by some recent work of Professor Brodie and Dr. Culler of Toronto, who have shown that, as regards the reflex action of vomiting, the vagus is the only afferent path from the stomach.

But cephalgia is not the only pain referred from the stomach: in gastric colic the pain is most distinctly felt over the chest—"breast-bone pain"—which is held to be explained by the fact that the visceral afferents from the stomach enter the spinal cord by the fourth and fifth dorsal segments, the same whereby somatic afferents from the sternal skin also enter it. Now the view that gastric colic rather than gastric catarrh should affect the afferent fibres from the stomach, is quite in accordance with the conclusions come to by Dr. Hertz, of London, who has made a special study of visceral sensation and pain (*Lancet*, April 29th, 1911). Dr. Hertz believes that fibres afferent from the muscular coats of the viscera are the fibres whose stimulation is the basis of visceral pain; distension and dysperistalsis, rather than any conditions of the mucosæ, being the *adequate* stimuli for hollow viscera. He quotes Professor Langley to the effect that most of the afferent sympathetic fibres of the intestine arise in the muscular coat: thus it is evident why afferent impulses from the visceral muscle in spasm traverse the abdominal

autonomic system and so affect segments concerned in "the dorsal outflow," whereas any irritation ascending by the vagus, and presumably from the mucosæ, is referred to cephalic skin-areas. The double, afferent, autonomic supply thus explains why such an organ as the stomach can give rise to referred pain in such widely separated parts as the head and the mid-region of thoracic skin.

A similar problem presents itself in the case of the heart which has a double innervation at least on the efferent side, namely, through the vagi and the cardio-accelerators of the sympathetic system. The afferent innervation is not nearly so well known: the depressor nerve of Ludwig and Cyon, afferent fibres reaching the nucleus of the vagus, is one path, but whether there are any afferent fibres entering by the "dorsal outflow" is still a matter of doubt. Their existence must, however, be postulated, because of the frequency of pain in the left arm in left cardio-valvular disease. Here the pain is referred to the cutaneous distribution of the intercosto-humeral branch of the second intercostal nerve, a branch of the second dorsal. Now we know that the cardiac dorsal outflow on the efferent side is through the second and third dorsal nerves, and presumably the cardiac inflow is by the same nerves.

Some writers have virtually suggested that the afferent impulses in cardiac irritation are ascending the efferent sympathetic neurones (cardio-accelerators); but this is physiologically improbable, since it involves the supposition that anti-dromic influences could not only ascend these efferent neurones but also pass over their cells of origin in the medulla (cardio-accelerator centre), and thus break the law of "valve-action" at a synapsis.

We might now ask ourselves, Is there any evidence to point to the kind of fibre, physiologically considered, which is concerned in the reference of pain to the skin? From the skin there are at least two kinds functionally. (1) Those subserving the sense of touch, the "epicritic" of Head. (2) Those concerned in painful sensations, and in those of heat and cold, the "protopathic" of Head.

That the paths from skin into the central nervous system for touch, on the one hand, and for pain and heat and cold, on the other, are different, is pretty well established: when pain is absent the thermæsthetic sensations are also, and vice versa. But touch may be retained when the other two sets of sensation are abolished, and vice versa.

Now we have a good deal of evidence to the effect that the peripheral distribution of tactile fibres is not the same as that of

pain and heat and cold fibres. Professor Sherrington showed that the section of one posterior root did not abolish touch in any one given cutaneous area; in order to produce complete anæsthesia there one must cut through several adjacent posterior roots. The impossibility of producing anæsthesia by the section of only one root is due to the fact of "overlapping innervation." The tactile innervation of any given skin-area is, then, from more than one segment of the cord; and, as might be expected, the areas of tactile anæsthesia are irregular in outline.

Sharply contrasted with this is the state of matters of the protopathic fibres—the algesic and the thermæsthetic. When, in disease of contiguous spinal cord segments, there are present areas of painless skin, it is found that these analgesic zones do *not* overlap, and it is also known that the areas in herpes zoster do not overlap. According to researches of Dr. Head, the areas of referred tenderness or pain in visceral disease are characterized by their not overlapping. The area of loss of pain is always more definite and more extensive than that of the loss of touch. Dr. Head has also pointed out that the centre of an area of referred pain is not only hyperalgesic, that is, more sensitive to real local pain, but it is also hyperthermæsthetic, or more sensitive to heat; this Dr. Head calls "the maximum spot." Taking all the facts just mentioned into consideration, we seem to be able to affirm that referred pain is related peripherally to those fibres from the skin concerned in the sensation of pain and heat and cold; and that the central mechanism of the transference is in segments of the grey matter of the cord and neither in the posterior roots nor their ganglia. If any impulses related to referred pain actually reach the periphery, as some imagine they do, and are of an atrophic nature, they must certainly be antidromic in these algesic fibres.

History: Referred pain, as "sympathetic" pain, figures pretty conspicuously in the history of ideas regarding the functions of "the nerves of vegetative life," as the autonomic nerves were for so long called. The presence of ganglia on the abdominal sympathetic nerves was known to Galen. How the term "sympathetic" came to be applied to the nerves now so called, seems to have arisen somewhat in the following way: actions, which we now call voluntary were known to be carried out by the cerebro-spinal nerves, so that apparently those actions known as sympathetic were carried out by the ganglionated nerves. Sympathetic activities included those we know as reflex as well as cases of referred tenderness and pain.

Thus, if we take such a work as Bostock's "Elementary System of Physiology," (London, 1836), we find the following described as sympathetic: (1) True reflex actions; the examples given being vomiting from irritation of a biliary calculus and contraction of the diaphragm in sneezing. (2) Cases of referred pain, the examples given being headache from dyspepsia, and pain in the shoulder from liver disease. (3) Abnormal (hysterical) mental conditions, epidemic mental affections, induced by personal fascination or by imitation of fanatics or by "personal magnetism" (Adam Smith, Dougald Stewart, and Alison). Also such imitative states as epidemic dancing and the mutilating manias of the Middle Ages.

As regards referred sensation, the condition had been noticed nearly one hundred years before by that extraordinary observer, the Rev. Stephen Hales (1727).

The views held at the close of the eighteenth century as to the offices of sympathetic nerves and their ganglia, can be learned from Prochaska's work, "The Functions of the Nervous System." Prochaska adopted the view that ganglia on nerves impede or obstruct sensory impressions ascending the nerves. This seemed reasonable from the apparent fact that we have no sensations from certain internal organs whose nerves have ganglia on their course. The converse of this, that the mind could not affect the viscera, because their efferent nerves passed through ganglia, seems to have originated with Tissot (1728-1797). Prochaska wrote, "The mind has no immediate control over the heart, stomach, and intestines, because the impressions made by the will on the origins of the nerves do not appear to be able to pass through the ganglia of the great sympathetic nerve." This false doctrine of the blocking of impulses by ganglia was held to apply to ganglia on cerebro-spinal as well as those on autonomic nerves, which explains Prochaska writing as he did thus: "He who shall unravel the uses of the ganglia will also give a reason why the fifth pair of cerebral nerves pass through the semi-lunar ganglion . . . . and why only the posterior roots of the spinal nerves enter the ganglia, whilst the anterior roots pass by without any communication with them." This was exactly what Magendie had explained by 1822. So competent a student of the nervous system as Reil, in the year 1811, the year of the publication of Bell's first pamphlet on the functions of the two roots, stated his belief in the blocking doctrine. By 1822 Magendie had demonstrated with great experimental fulness the law of the two roots, that the anterior was efferent only, and the posterior afferent only. Bell had already made it clear

that the Gasserian ganglion was the analogue of the posterior spinal ganglia, and that neither the one nor the others interfered with impulses going into the brain or spinal cord. But the ganglia, especially the sympathetic, had been for long credited with a positive function, namely, that of being the set of reflex actions. Although, of course, the term "reflex" was not in all cases used, Vieussens, Hermann Boerhaave, Vater, Meckel, and Gasser all believed that nerve-impulses (though they did not employ that term) were turned back towards the periphery at the nerve-plexuses and ganglia.

Prochaska puts it clearly thus: "Further, it may be asked whether the external impressions made on the terminations of the nerves and passed onwards to the ganglia are extinguished in the ganglia themselves, or whether being reflected there by a fixed law they return again along the nerves to the parts to be moved." Long after sympathetic ganglia were shown to be composed of nerve-cells, the possibility of their being reflex actions was believed in, but Professor Langley, who has gone into this question with considerable care, has come to the conclusion that there is no unequivocal example of a reflex action being carried out through the intermediation of any peripheral ganglia, with the possible exception of the enteric ganglia.

Both the original surmises as regards the ganglia have been shown to be incorrect, they neither block afferent impulses nor do they mediate reflex actions; the prophecies concerning their functions have proved peculiarly unfortunate. Some guesses in science have been subsequently proved right, those as to the sympathetic system and ganglia generally have not been of this order.