THE CROONIAN LECTURES ON SOME POINTS IN THE PATHOLOGY OF RHEUMATISM, GOUT, AND DIABETES.

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LECTURE II.

WHAT in rheumatism is the starting-point of the morbid process? Is there such a thing as the rheumatic poison; if so, what is it? and what is the nature of the change which takes place as the result of its action? Let me, in the first place, enumerate the more salient features of the disease, as gleaned from clinical experience. An individual, after feeling out of sorts for two or three days, perhaps after a chill, wakes up in the morning with one of the joints stiff and tender; soon afterwards it swells, and motion causes pain. Other joints now become affected; the knees, wrists, elbows, ankles, and the smaller joints of the hands and feet. There are pain, tenderness, increased heat, swelling, and redness of the skin. The tendency of these to shift from joint to joint is a remarkable feature of the disease. The slightest motion becomes insupportable; even vibration of the room or of the bed causes suffering. There is more or less febrile movement, the temperature ranging from 102° to 104° , or higher, generally more or less sweating, the odour of which is characteristic. The tongue is coated; thirst is generally a marked symptom; and the urine is turbid with lithates, and has a strong acid reaction.

The more acute and severe the case, the more profuse and acid is the perspiration, and the larger the amount of lactic acid which it contains.

This last feature has led to the supposition that, in acute rheumatism, there is excessive formation of this acid, which, circulating through the system, gives rise to the symptoms which accompany the disorder. It is a theory which has got a very firm hold of the minds of many physicians, and is probably the one most generally adopted. There is so much to be said in its favour, that, until recently, I unhesitatingly accepted it. I hope to show now that, though lactic acid is formed in excess in the disease, and its presence in the blood modifies the symptoms in some degree, it is not the chief agent in producing them. Other factors are at work giving rise to the characteristic feature of rheumatism, namely, the affection of the joints, as well as to some of the other symptoms which I have enumerated; and the excessive formation of this acid must be regarded more as one of the symptoms than as the cause which gives rise to them.

The lactic acid theory, however, has furnished me with my true starting-point. In attempting, five or six years ago, to arrive at some satisfactory explanation of the phenomena of this disorder, the line of argument which suggested itself to my mind was much as follows.

1. Lactic acid is the *materies morbi* in rheumatism.

2. According to the views of some authorities, the natural source of lactic acid in the system is glucose, which is first transformed into lactic acid, and then further oxidised into carbonic acid and water.

3. By the so-called "diabetic puncture" the metabolism of glucose in the system can be arrested; sugar appears in the urine, and we have the phenomena of diabetes.

Changes, therefore, in the medulla oblongata entirely arrest the metabolism of glucose; and if so, if this is true, would it be possible by modifying these changes in the medulla partially to arrest the transformation of glucose into CO_2 and H_2O at the intermediate stage of lactic acid, and so develop rheumatism? That is to say, have neurotic conditions, have changes in the medulla oblongata,

anything whatever to do with the symptoms which are associated with rheumatism?

These were the hypotheses with which I started; but I have tried to show in my previous lecture that lactic acid in the tissues is formed, not from glucose, but from the nitrogenous molecules of the tissues, namely, the cyan-alcohol $\text{CH}_3 \cdot \text{CH} \left\{ \begin{array}{l} \text{OH} \\ \text{CN} \end{array} \right.$ and $\text{CH}_2\text{CH}_2 \left\{ \begin{array}{l} \text{OH} \\ \text{CN} \end{array} \right.$. My second hypothesis, therefore, falls to the ground, and with it the third to a very large extent. Certain points, however, presented themselves to me during the consideration of the subject, which seem to connect the disorder with changes in the nervous system, and to furnish a theory as to the causation of rheumatism, by which an explanation may be offered not only of the way in which the symptoms are produced, but also of the action of some of the remedies which have been successfully employed in the treatment of the disease. To these points let me now specially invite your attention.

As a first step in demonstrating the connection of rheumatism with changes in the nervous system, let me refer to some nerve-lesions which are associated with changes in the nutrition of the joints. In respect to this, I find that more than fifty years ago the late Dr. J. K. Mitchell¹ advanced a theory of the pathogenesis of rheumatism which connected it with affections of the spinal cord. My own view, which localises the controlling action of the nervous system in the disorder chiefly in the medulla oblongata, was formed quite independently; it was only, in fact, quite recently that my attention was directed to Dr. Mitchell's views by finding a reference to them on reading a most admirable work, abounding with interesting facts, by his son, Dr. Weir Mitchell, on *Injuries of Nerves*. I here discover, however, some most important links in the chain of evidence supporting my theory, which I will place before you; and, after referring to other cases of a similar kind, I shall then attempt to point out the way in which the nervous centre is affected, both in gout and in rheumatism—how, in fact, the rheumatic poison is developed, and how it acts.

In a work on *Gunshot Wounds and other Injuries to the Nerves*, by Drs. Weir Mitchell, Moorhouse, and Keen, of the United States Army², there is the following statement:

"Alterations in the Nutrition of Joints.—Again we call attention to a peculiarity of nerve-injuries, which we believe to have been overlooked.

"Like the altered nutrition of the skin, the symptom which we are at present considering occurs at any time after the first few days. It consists essentially in a painful swelling of the joints, which may attack any or all of the articulations of a member. It is distinct from the early swelling due to the inflammation about the wound itself, although it may be masked by it for a time; nor is it merely a part of the general oedema which is a common consequence of wounds. It is more than these—more important, more persistent. Once fully established, it keeps the joints stiff and sore for weeks or months. When the acute stage has departed, the tissues about the articulations become hard, and partial ankylosis results, so that, in many cases, the only final cause of loss of motion is due to this state of the joints. Of all the agencies which impede movement, it is the most difficult to relieve.

"Were we asked to state in what essential respect these lesions differ from subacute rheumatic disease of the same parts, we should certainly be at some loss to discern a difference.

"The subject suggests certain interesting reflections. We have ourselves seen cases of spinal injury, in which rheumatic symptoms seemed to have been among the consequences; and four such instances of striking character are to be found recorded in a paper by the late Professor J. K. Mitchell, in the *American Journal of the Medical Sciences*, vol. viii, p. 55. Upon the hints which were thus furnished, Dr. Mitchell was induced to consider rheumatism as of spinal origin. His treatment,³ founded on this view, was most successful, and is still used and recognised in this country. Modern pathologists have traced the causation of rheumatism to a strictly chemical source; but no one can avoid seeing that there may be a cause beyond this, even though the chemical conditions be still considered as essential links in the chain. Thus, after all, the true origin may be spinal, or, at all events, the indisputable fact that there are rheumatisms depending for existence on neural changes, may aid us hereafter to discriminate varieties of type among the forms of rheumatic disease.

¹ The American Journal of Medical Sciences, 1831, vol. iii, p. 55.

² Gunshot Wounds and other Injuries of Nerves. By Drs. Weir Mitchell, Moorhouse, and Keen. Philadelphia, 1864. Pp. 85–85.

³ The treatment he adopted was to apply from eight to sixteen cups, abstracting about as many ounces of blood, to the cervical or lumbar spine, according as the upper or lower extremities were affected, and follow the cupping, if this did not afford relief, by the application of blisters to the spine.

It were easy to dwell upon this subject, but enough has been said to show that subacute inflammation of joints may be brought about by nerve-lesions, and to direct medical thought anew in a direction which seems favourable to its true and rational progress."

In a subsequent work—the work to which I have already referred—*On Injuries of Nerves*,⁴ Dr. S. Weir Mitchell writes: "Of all the various forms of mischief wrought by nerve-wounds, the most intractable and disabling are the curious inflammatory states of joints to which we were the first to call attention."

"In a certain number of nerve-wounds, notably most often in those of the upper extremities, one or more of the joints in the wounded limb become swollen. The nature of the injury does not seem to influence the case, as I have seen it follow dislocations, ball-wounds, and contusions of nerves; while, in an interesting case of Dr. Packard's, it was one of the consequences of compression of the sciatic nerve by a tumour. More lately, in the service of my friend Dr. J. A. Brinton, at the Philadelphia Hospital, I saw a man who had extensive joint-lesions, owing to the brachial nerves having suffered during the dislocation, or upon the subsequent reduction, of the humerus, so that I suspect these troubles are more common than has been supposed.⁵ In one case the joints of the fingers became swollen and tender on the third day after ball-wound of the brachial plexus, but usually the swelling appears much later, and, like the glossy skin, is frequently the offspring of secondary neuritis. Often masked at first by the general inflammation of the limb, or concealed by the oedema so common after nerve-wounds, it is more persistent than these, and, as they fade, begins to assume importance. We may then have one articulation—and if only one, a large one—involved, or perhaps all the joints of a finger, or every joint in the hand, or of the entire limb may suffer. The swelling is never very great, the redness usually slight, and the tenderness on touch or motion exquisite. This condition of things remains, with little change, during weeks or months, and then slowly declines, leaving the joints stiff, enlarged, and somewhat sensitive, especially as to movement. A small proportion of such cases find ready relief, but in many of them the resultant ankylosis proves utterly unconquerable, so that it is vain to break up the adhesions under ether, or to try to restore mobility by manipulation on splints. All alike fail, and serve only to add to the essential tortures of the accompanying neuralgia and hyperæsthetic states of skin. Since writing my last paper,⁶ I have met with some of the former patients who suffered with these troubles, but in no case originally very severe was there any great gain; indeed, in most of them the joints had become every year more stiff and useless.

"It is then quite clear that injuries of the spine, diseases of this organ, and of the brain, and wounds, or any form of lesions of nerves, are capable of developing in the joints inflammatory conditions, usually subacute, and which so precisely resemble rheumatic arthritis in their symptoms and results, that no clinical skill can discriminate between the two. In this state it were well to leave the subject. The chemical theories have crumbled, and, in the growing tendency to believe that rheumatism may have more forms than one, it may not be amiss to recall the facts to which we have contributed, and which are well illustrated by the following case. Other and more severe examples will be found in the cases appended to the later chapters of this work.

"CASE 30.—*Gunshot Wound of the Right Brachial Plexus: Causalgia: Tremor: Arthritic Lesions: Nail-Changes: Acid Sweats: Hyperæsthesia: Little Loss of Motion from Paralysis: Great Gain under Treatment.*—B. D. L., aged 43, a farmer from Maine. Enlisted July, 1862. He was healthy to the date of his wound, received July 2nd, 1863, at Gettysburg. While kneeling and aiming, he was shot in the right side of the neck. He felt pain in the wound, but none down the arm. He spun round, feeling stunned, and fell on his back, not unconscious. In five minutes he rose and walked to the rear, where the wound was dressed with cold water, no splint being employed either then or later. At first, all motion was lost. In an hour he could move his finger and abduct the arm, but not flex it. He thinks sensation was perfect, except as to the ulnar distribution. Within an hour, he had severe earache, and pain in the shoulder, arm, and forearm. During the second week, he began to have burning pain in the hand. At this time, which probably marked the onset of neuritis, the shoulder-joint grew stiff, then the elbow, and lastly all of the fingers. This condition was excessively painful, and remained unchanged. The tremor, which is constant in the upper arm muscles, began the day of the wound, and had not ceased on his admission to our wards.

⁴ London and Philadelphia, 1872, pp. 108-172.

⁵ I have since met with similar cases.

⁶ Reports of the Sanitary Commission.

"*Site of Wound.*—On admission, October, 1863, it was noted that the ball had entered the right side of the neck, in front, three inches above the clavicle, in the outer edge of the trapezius. The missile passed downward and outward, and struck the anterior edge of the supraspinal fossa of the scapula, five inches external to the spine of the first dorsal vertebra. Both wounds sloughed, leaving scars one and a half inches in diameter. The patient is well and florid. The shoulder is motionless from stiffness. The lower joints are alike stiff, swollen, red, and painful: the arm, semi-prone and flexed, is carried across the chest, supported by the sound hand. He has slight motion throughout, but the effort caused fibrillar tremor and exquisite pain.

"*Sensation.*—The sense of touch is everywhere good, save that there is slight numbness of the back of the hand and forearm. Some causalgia is felt in the palm, but no other pain, except on movement.

"*Nutrition.*—The palm is thin and red, or purplish, and on it the patient uses water, now and then, as a dressing; there is no atrophy; the wound is healed, but tender, as are also the upper nerve tracks. Muscular hyperæsthesia of the deltoid and triceps is present. The nails are remarkably curved; the hair is scanty; the sweat ill-smelling and acid. The shoulder muscles alone have lost electro-muscular contractility (induction current). Under ether, the joints when moved are found to be free from well-marked organic adhesions.

"Passive motion and electricity caused speedy gain in movement, and in February, 1864, he was able to move all the joints, with diminished pain. The muscles were, at this time, sensitive to induced currents, and the numbness and causalgia had nearly disappeared. He was allowed a furlough, at the expiration of which he deserted.

"This case is valuable, as an example of arthritic changes, extreme in character, with very little sensory or motor paralysis, and seemingly aided by treatment."

Again, Sir William Gull⁷ has recorded the two following cases, and his remarks upon them are so suggestive, that I quote them in full.

"CASE 27.—*Acute Rheumatic (?) Affection of the Larger Joints: Paraplegia of Lower Extremities: Slough over Sacrum: Recovery.*—Anne E., aged 38, was admitted into Guy's Hospital, March 31st, 1857, under the care of my colleagues, Dr. Hughes and Dr. Wilks (to whom I am indebted for placing the case at my disposal). Both hands were swollen, stiff, and painful, with an erythematous blush over the back of the right, and on the second joint of the thumb of the left. The legs were so far paralysed that she could only very slowly and feebly move them. The muscles were greatly wasted and flabby, but had not lost their excito-contractility by galvanism. Sphincters weak. No swelling of the knees or ankles at this time. Sensation nearly normal; but at times both legs felt numb, and were drawn up involuntarily. Urine acid, high coloured, and scanty. Tongue covered with a cream-like fur; skin hot; perspiration profuse, with acid smell. Pulse 120; systolic murmur over ventricle. On examining the spine, the lower third of the sacrum was found to be bent forward, the result of a fall eleven years before; and near the sacral notch, on the right side, was the cicatrix of a wound which formed at that time. Except this, there was nothing abnormal, nor any pain or tenderness on pressure. The history she gave of her case was that, being a widow, she was necessitated to work laboriously at a mangle. She had for two years, when much exerting herself, felt pain in the back between the shoulders, and a sense of constriction and coldness round the chest. Ten days before coming into the hospital she was seized with pain in the left leg, and had spasmodic contraction of the muscles, with an increase of the pain and constriction round the chest. She had still power to extend the leg, but could not walk. The day following, the hand, knees, and ankles were swollen and painful. With these symptoms there was febrile heat and diarrhoea. The sphincter ani was so weak that the feces ran from her involuntarily. On the third day a slough formed over the sacrum. No important change occurred in her symptoms after her admission. There was great muscular emaciation generally. Involuntary twitchings of the muscles of the arms and legs. Aching, gnawing sensations in both calves. Touching the feet gave rise to formication and very lively excito-motor movements. For ten days the hands remained red, painful, stiff, and swollen. She complained much of heat and profuse perspirations, which returned several times in the twenty-four hours. On April 8th the urine was ammoniacal, and contained mucus. The hands were still swollen and erythematous; face flushed; pulse 100, full, as in rheumatism; acid smell of

⁷ Guy's Hosp. Reports, 3rd Series, vol. iv, 1858, Cases 27 and 28.

perspiration; respiration 28; movements thoracic and abdominal; abdomen soft; pupils large; nights sleepless. Ordered a grain of opium every six hours, with six ounces of wine daily, and a chop. On April 18th, the good effects of the opium and support were very apparent. The patient had passed good nights, and was tranquil in the day. Perspiration lessened. Urine retained in the bladder for thirty-six hours was at length passed voluntarily; it was acid, and without mucus. Tongue pale and moist. The slough on the back had deepened. The pupil still continued large. Occasional contraction of the muscles of the legs; no permanent rigidity. Hands remained swollen and stiff, but less red. She was unable to move the shoulders freely. On April 22nd, the hands had recovered their normal appearance, and had lost their stiffness. The legs could be moved more freely. The sense of constriction round the chest was gone; pulse 96; skin cool and dry; appetite good; urine normal, but she could not empty the bladder oftener than once in twenty-four hours. From this date, she slowly recovered. The opium was continued throughout her convalescence. At the beginning of June, the muscles of the lower extremities were galvanised regularly. By the end of the month, she was able to stand without help. Her improvement was uninterrupted, and in September she left the hospital quite well.

REMARKS.—It is a matter of great clinical interest that lesions of the cord are occasionally attended with an affection of the joints not to be readily distinguished from that which occurs in acute rheumatism. When this happens, there may be difficulty in determining the pathology of a case. It may, indeed, be impossible to say whether the symptoms at a certain stage are due to disease of the cord or to a rheumatic state of the blood. In such instances, we have a proof of the near relation of humoralism and solidism; for one observer may maintain that the local lesions have a common origin in the altered state of the blood, whilst another may with equal confidence assert their dependence upon a primary disturbance of the nervous centres. The case here recorded is an example of these difficulties. Fatigue from mechanical labour, acting especially on the lumbar and dorsal portions of the spine in a delicate and anxious subject, appears to have injured the nutriment of the cord. For two years, when much exerting herself, the patient felt pain between the shoulders, and a sense of constriction and coldness round the chest. Paraplegia then suddenly came on, followed by redness, pain, and swelling of the larger joints, as in rheumatism. Together with these symptoms, there were others indicating a rheumatic condition—white furred tongue; flushed face; hot skin; profuse perspirations, having an acid smell; systolic murmur over left ventricle, etc. Was there here a rheumatic state of the blood induced by the spinal lesion; or was the nervous derangement the result of a rheumatic state? Notwithstanding the labours of morbid anatomists and chemical pathologists, we are not at present in possession of any certain knowledge of what constitutes the rheumatic condition. My colleague Dr. Addison, from his clinical experience, has long drawn attention to the close connection between spinal lesions and true rheumatism, but has never developed the idea beyond expressing a suspicion of their relation. At the time this case was under care, the treatment was a subject of much observation. The result was very satisfactory. Whatever might have been the state of the cord, it was clearly induced by fatigue, and was soon followed by sloughing of the integuments. It would not, therefore, admit of depletory measures, but, on the contrary, required a nutritious diet, and wine. Opium was prescribed apparently with great advantage; it allayed nervous irritability, and gave the patient sleep.

The following case is also illustrative of the relation between spinal injury and rheumatic symptoms. The same plan of treatment as above was equally successful. The therapeutical view of this subject is certainly not without the greatest interest. No doubt the texture of the cord has but feeble reparative powers, notwithstanding it has been shown by experimenters on animals that occasionally, after a transverse section, the parts unite, and the functions are re-established.

CASE 28.—*Concussion of the Spine: Partial Paraplegia: Redness and Swelling of the Wrists and Ankles as in Acute Rheumatism: Recovery.*—N. T., aged 38, on January 22nd, 1885, inadvertently stepped backwards into a hole, a few feet deep, and received a concussion of the spine. After a few days, he became partially paraplegic, with weak sphincters; and at the same time there came on a diffused redness and swelling of the ankles and wrists. The swelling was not from effusion into the joints, but from oedema of the surrounding tissues. The joints were very painful. The redness and swelling were variable in degree. When most marked, they presented the usual appearances of rheumatism, or rather of gout, for the erythema

was brighter, and the oedema more distinct than in rheumatism. The hands equally affected with the ankles, though there was no obvious want of muscular power, nor any affection of sensation in the upper extremities. Tongue clear. Pulse 120. No acid perspirations. Urine high coloured, free from deposits, of normal quantity. The nerves of the surface generally were hyperæsthetic to a slight touch, but deep pressure gave less inconvenience. The treatment consisted of good nourishment, wine and brandy freely administered, and opium to allay pain and overcome sleeplessness. The pulse gradually acquired more power, and sank to 80. The affection of the joints continued in varying degree through March, April, May, and June. From the beginning of April, there was an improvement in the power over the legs. The same treatment was continued throughout, without the use of mercurials, local depletion, or counter irritation. In June, the patient was able to walk without assistance. During sleep, the hands and feet, wrists and ankles, often become erythematous and swollen. There was occasional formication in the lower extremities. Sleeplessness, from the beginning of the case, and throughout, was a troublesome symptom. In July, the patient was able to leave the hospital, and to resume to some extent his duties as medical practitioner. He was under the care of my colleague Mr. Cock.

Again, according to Professor Charcot, "nutritive disorders consecutive on lesions of the nervous centres not unfrequently take up their seat in the articulations." He establishes two varieties. The first comprises such cases as those to which I have already referred, and includes here, also, the arthropathy of hemiplegic patients, first described, in 1846, by Scott Alison,⁹ afterwards by Brown-Séquard.¹⁰ These "arthropathies" are limited to the paralysed limbs, and mostly occupy the upper extremities. They supervene, especially after circumscribed cerebral ramollissement, and more rarely as a consequence of intra-encephalic hæmorrhage.

"They usually form fifteen days or a month after the attack of apoplexy; that is to say, at the moment when the tardy contracture that lays hold on the paralysed members appears; but they may also show themselves at a later epoch. The tumefaction, redness, and pain of the joints are sometimes marked enough to recall the corresponding phenomena of acute articular rheumatism. The tendinous sheaths are, indeed, often affected at the same time as the articulations.

"It is needless to insist upon the interest which pertains to these arthropathies as regards diagnosis—articular rheumatism, whether acute or subacute, being an affection often connected with certain forms of cerebral softening, and one which, indeed, shows itself also, occasionally, after traumatic causes, capable of determining shock in the nervous centres. On the other hand, many affections of the spinal cord are erroneously attributed to a rheumatic diathesis in consequence of the coexistence of these articular symptoms. The clinical characters which render it easy to recognise arthropathies correlated with lesions of the nervous centres, and which allow them to be distinguished from cases of rheumatic arthritis, are chiefly these:

"1st. Their limitation to the joints of the paralysed members.

"2nd. The generally determinate epoch in which, in cases of sudden hemiplegia, they make their appearance on the morbid scene.

"3rd. The coexistence of other trophic troubles of the same order, such as eschars of rapid formation; and (when the spinal cord is involved) acute muscular atrophy of the paralysed members, cystitis, nephritis, etc.

"The type of the second group is to be found in progressive locomotor ataxy.....

"Ataxic arthropathy usually occupies the knees, shoulders, and elbows; it may also take up its seat in the hip-joint."

Professor Charcot then goes on to describe the physical and clinical characters of this form of arthropathy; and, after pointing out the absence of all traumatic or diathetic cause of rheumatism or of gout, he proceeds as follows:

"It is not very rare to find the spinal grey matter affected in locomotor ataxy; but the lesion is then generally found in the posterior cornua. Now, it was quite different in two cases of locomotor ataxy, complicated with arthropathy, in which a careful examination of the cord has been made; the anterior cornua were, in both cases, remarkably wasted and deformed, and a certain number of the great nerve-cells, those of the external group especially, had decreased in size, or even disappeared altogether without leaving any vestiges. The alteration, besides, showed itself exclusively in the anterior cornua, corresponding to the side on which the articular lesion was situated. It affected the cervical region, in the first case, where the arthropathy

⁹ *Lectures on Diseases of the Nervous System.* Translated by Dr. Sigerson. New Sydenham Society, 1877, p. 92.

¹⁰ "Arthritis occurring in the course of Paralysis." *The Lancet*, vol. i, p. 278, 1846.

¹¹ *Ibid.*, July 13th, 1861.

occupied the shoulder; it was observed a little above the lumbar region in the second case, which presented an example of arthropathy of the knee. Above and below these points, the grey matter of the anterior cornua appeared to be exempt from alteration.

"From what precedes, I hope to have made it appear at least highly probable that the inflammatory process, first developed in the posterior columns, by gradually extending to certain regions of the anterior cornua of the grey matter, was able to occasion the development of the articular affection in our two patients. If the results obtained in these two cases are confirmed by new observations, we should be naturally led to admit that arthritic affections connected with myelitis, and those observed to follow on cerebral softening, are likewise due to the invasion of the same regions of the grey matter of the spinal cord. In cases of brain-softening, the descending sclerosis of one of the lateral columns of the spinal cord might be considered as the starting-point of the diffusion of inflammatory work."

From these illustrations, gathered from various authorities, it is, I think, very clearly shown that lesions in the spinal cord, or along the course of the motor nerves, may give rise to changes in the joints, which, in many cases, present no difference from the condition seen in subacute rheumatism; in others, as in Charcot's disease, producing rapid disintegration of the bony tissue, decay without repair, as it has been aptly termed by Morrant Baker. But in all the cases we have changes taking place in the condition of the joints, and these changes produced by causes acting on the nerves connected with the part, either along the course of these nerves, or at their origin in the central nervous system.

Now, is there in the phenomena of rheumatism anything suggestive of an irritating cause acting upon portions of the central nervous system? If so, what is it, and how is it produced?

Let me call your attention to the changes produced in the system when, under the normal state of things, the surface of the body is exposed to the action of cold or heat. The effect, as is well known, is very different as regards cold-blooded and warm-blooded animals. External cold diminishes and heat increases the metabolic activity of the cold-blooded animal, acting like a mixture of dead substances in a chemical retort. But in a warm-blooded animal, within certain limits, cold increases and heat diminishes the bodily metabolism, as shown by the increased or diminished consumption of oxygen, and production of carbonic acid, as the temperature falls or rises. There is obviously a mechanism of some kind counteracting, and indeed overcoming, those more direct effects which alone obtain in cold-blooded animals. But, under the influence of urari, which paralyses the end-organs of the muscular nerves, a warm-blooded animal behaves, as regards its bodily metabolism under the influence of external cold and heat, like a cold-blooded animal. A similar result is obtained by division of the medulla oblongata. The temperature of an animal so operated upon falls, and then exposure to heat augments, and exposure to cold diminishes, its metabolic activity. "We can best explain these results by supposing that, under normal conditions, the muscles which, as we have seen, contribute so largely to the total heat of the body are placed, by means of their motor nerves and the central nervous system, in some special connection with the skin, so that a lowering of the temperature of the skin leads to an increase, while a heightening of the temperature leads to a decrease, of the muscular metabolism. Further, though the matter has not been fully worked out, the centre of this thermo-taxis reflex mechanism appears to be placed above the medulla oblongata, possibly in the region of the pons Varolii. When urari is given, the reflex chain is broken at its muscular end; when the spinal cord is divided, the break is nearer the centre."¹¹

How does this bear upon rheumatism? An individual is exposed to a cold draught or gets wet; the surface is chilled; the cutaneous vascular areas are constricted; by reflex action through the vaso-motor system, the splanchnic vascular areas and the vessels of the muscular areas are dilated; the vaso-motor nerves distributed to these parts are paralysed, so to speak; with this paralysis of the vaso-motor nerves there is dilatation of the vessels in connection with them, and so a large amount of blood is carried to the part, and consequently a larger quantity of oxygen to act upon the tissues. But an increased supply of blood is not sufficient of itself to increase the functional activity of an organ, and therefore to produce increased heat. This has been clearly demonstrated by the well known experiments on the submaxillary gland, and by the experiments on the muscles. The submaxillary gland is supplied by two nerves, the branches of the chorda tympani reaching it along its duct, and by branches of the cervical sympathetic reaching it along its arteries. Now the chorda contains two sets of fibres, (i) secreting fibres acting

only on the epithelium cells, and (ii) vaso-motor or dilating fibres. Stimulation of this nerve brings about two events, dilatation of the blood-vessels of the gland and a flow of saliva; that is, there is not only a dilatation of the vessels, and so increased supply of blood, but there is an absorption, an assimilation, of some of the molecular constituents of the blood by the gland cells; and, if these constituents are properly elaborated by the cells, the formation of saliva. But the elaboration of these constituents can be modified, for by stimulating the sympathetic nerve "a slight increase of flow is seen; but this soon passes off, and so much saliva as is secreted is remarkably viscid, of higher specific gravity, and richer in corpuscles and protoplasmic lumps, and is said to be more active on starch than chorda saliva."¹² This fact has a very important bearing upon the subject I am discussing—the fact, namely, that, according to the variations in the stimulus applied to the two sets of nerves, alterations in the secretion can be produced: modification, that is to say, in the molecular changes in the contents of the secreting cell can, in this way, be brought about.

Further, if a small quantity of atropin be injected into the veins, stimulation of the chorda tympani produces no secretion of saliva at all, though the dilatation of the blood-vessels takes place as usual. This proves "that atropin, while it has no effect on the vaso-motor fibres, paralyses the secreting fibres just as it paralyses the inhibitory fibres of the vagus. Hence, when the chorda is stimulated, there pass down the nerve, in addition to impulses affecting the blood-supply, impulses affecting directly the protoplasm of the secreting cells, and calling it into action, just as similar impulses call into action the contractility of the protoplasm of a muscular fibre. Indeed, the two things, secreting activity and contracting activity, are quite parallel. We know that, when a muscle contracts, its blood-vessels dilate; and, just as by atropin the secreting action of the gland may be isolated from the vascular dilatation, so by urari muscular contraction may be removed, and leave dilatation of the blood-vessels as the only effect of stimulating the muscular nerve."¹³

If this is the case, there must be, in order that heat may be developed, not only an increased supply of blood to a tissue, but also some chemical change in its molecular constituents. Such a molecular transformation is shown by the production of lactic acid and carbonic acid, when a muscle contracts or when it dies. The molecules forming these substances are detached from the muscular tissue. Now, I would suggest that the change in the molecular constituents of the muscular tissue which leads to the further development of heat, results from a weakening or lessening of the power, whatever that may be, which holds the molecules together; that with the dilatation of the vessels in the part, under the influence of the vaso-motor nerves, there is also a splitting up or tumbling to pieces of the albuminoid molecules, and from both causes heat is developed. The normal change of the cyan-alcohols is interfered with. Their condensation into higher cyan-alcohols with elimination of urea, or their change into cyanamides and amido-acids, with the ultimate oxidation of the latter, is modified. The molecules $\text{CH}_2 \begin{Bmatrix} \text{OH} \\ \text{CN} \end{Bmatrix}$ and

$\text{C}_2\text{H}_4 \begin{Bmatrix} \text{OH} \\ \text{CN} \end{Bmatrix}$ become detached more or less from each other, and by hydration (by which heat is developed) form substances—glycollic acid and lactic acid—which are readily oxidised, more readily than the amido-acid glycocine which is also formed. The oxygen, though conveyed in larger quantities than normal by the increased blood-supply to the tissue, is completely used up in oxidising into carbonic acid and water, the glycollic and lactic acids¹⁴ which have been formed; the excess of lactic acid and the glycocine are unoxidised, and pass into the circulation. Now, in a normal or healthy state of things, the irritating or stimulating cause acting on the vessels and nerves of the skin being removed, reaction would be set up there, the cutaneous vascular area acted upon by the lactic acid would dilate, and consequently the vessels of the muscular area would contract; and this latter contraction would be increased by the stimulating effect of the glycocine, or some resulting morbid product, which, being a morbid product, would stimulate some portion of the nervous system. We should naturally expect that, under the normal state of things, it would so act upon the nervous system as to check the further formation of the morbid material. This could be done by stimulating the vaso-motor nerves connected with the vessels of the muscular area, and causing their contraction. We have such an example of stimulation, though in a different direction, in the effect of carbonic acid on the respiratory centre. A closer illustration may perhaps be found in

¹¹ Foster's *Physiology*, 4th ed., p. 467.

¹² *Ibid.*, p. 261.

¹³ *Ibid.*, p. 261.

¹⁴ See p. 635.

¹⁵ See p. 633.

this stage is shown very distinctly by the murexide test. In the earlier stages the murexide reaction is very faint indeed. In this way, though the yield is comparatively very small, I have obtained extremely well marked crystals presenting all the characteristics when seen under the microscope of ordinary uric acid, and responding perfectly to the murexide test.¹⁷

The following equation represents the changes :

But it is important to know what are the intermediate stages, if we are to understand the mode of formation of this substance in the living body.

Now, hydantoic acid has been formed synthetically, and here we have the first step towards the synthesis of uric acid. By heating urea and glycocine to a temperature of 120°–125°C., they combine and form hydantoic acid.¹⁸

and this dehydrated forms hydantoin ; for, by boiling the latter with baryta water, it is converted into hydantoin acid.

By heating urea alone to a temperature somewhat higher, namely, to 150°–160°C., condensation takes place, and it is converted into biuret $\text{C}_2\text{O}_2\text{N}_3\text{H}_3$.

If now we combine together hydantoin and biuret, we have the elements of water and ammonium urate :

In performing Horbaczewski's experiment, when the temperature is raised to 120°–125°C. hydantoic acid is formed, and at 130°–150°C. the urea condenses into biuret. If, then, between 130° and 160°C. the hydantoic acid is dehydrated into hydantoin, which melts at 207°, and, at that temperature, or one something above, combined with the biuret in the manner above shown, forming water and ammonium urate, we have a complete explanation of the process.

That the synthesis takes place in this way, I have confirmed in some measure by experiment. One part of hydantoin, with four parts of biuret, were treated in the same manner as in the experiment with urea and glycocine. Throughout, the same results follow as when operating upon glycocine and urea ; but the yield of uric acid is smaller. On evaporating the solution after the addition of hydrochloric acid, crystals are deposited which give the murexide reaction very distinctly, but as yet I have not been able to isolate the uric acid.¹⁹ The constitution of glycoluril $\text{C}_4\text{H}_6\text{N}_4\text{O}_2$ which can be obtained from uric acid, and from allantoin, also favours this view. By boiling glycoluril with acids it is converted into hydantoin and urea. Consequently, by combining these substances together in a suitable way, we ought to perform the synthesis of glycoluril.

If, then, hydantoin were combined with biuret instead of with urea, we should have

which is the molecular formula for uric acid given by Medicus, and the one most generally accepted.²¹

My explanation of the formation of uric acid in the animal economy, based on these considerations, is as follows:

In the human subject, glycocine conjugated with cholic acid is poured out as glycocholic acid, a constituent of the bile, into the intestine. After the bile has served its purpose in digestion, the glycocine as well as taurine are returned into the blood. These, together with the other amido-bodies, leucin, and possibly tyrosin, the products of the digestion of albuminous food, reappear in the urine as urea ; that is, the urine does not contain them, but its urea is proportionately increased. Now these amido-bodies, glycocine, leucine, etc., are probably carried by the portal vein straight to the liver, and, from certain facts which I need not here detail, we are led to the view that, among the numerous metabolic events which occur in the hepatic cells, the formation of urea from these bodies may be ranked as one. Suppose from some cause this metabolism of glycocine is interrupted (and I need only refer here to the interrupted metabolism of starch or glucose in diabetes as an illustration of what I mean), whilst taurine, leucine, etc., still undergo the normal changes with the production of urea, we should then have in the gland the two substances, glycocine and urea (or the immediate antecedent of urea) the conjugation of which by the gland (just as in the case of hippuric acid being formed from the conjugation of glycocine and benzoic acid) would produce hydantoic acid,

which dehydrated would be converted into hydantoin

²¹ This explanation of the synthesis of uric acid indicates, I think, the way in which guanine, xanthine, hypoxanthine, theobromine, and caffeine may each be built up from glycocine, and thus showing their relationship to uric acid. By

combining glycocine with formyl diamine $\text{CH} \begin{Bmatrix} \text{NH}_2 \\ \text{NH} \end{Bmatrix}$ which is prepared from

HCN , we should obtain the substance $\text{CH} \begin{Bmatrix} \text{NH}-\text{CH}_2 \\ \text{N}-\text{CO} \end{Bmatrix}$ and this, united with

two molecules of urea, or with biuret, would probably result in

From guanine the other bodies have been obtained ; but it would appear probable that they should be synthesised independently. By combining glycocine, formyl diamine, guanidine (obtained from biuret) and urea in the order given, xanthine would result. By acting on the compound of glycocine and formyl diamine so as

to obtain its methyl derivative $\text{CH} \begin{Bmatrix} \text{N} \cdot \text{OH}_2-\text{OH}_2 \\ \text{N}-\text{CO} \end{Bmatrix}$ combining this with dime-

thyl carbamide, and then with urea, the resulting product should be caffeine. I have not had time to attempt these experiments since this mode of synthesis occurred to me. I hope to do so, however, during the summer, and so either confirm or refute the hypothesis.

¹⁷ The solution of potassium sulphide must be pure. If on adding hydrochloric acid to the solution of uric acid in this, sulphurous acid is evolved, the uric acid is decomposed and not precipitated.

¹⁸ Heintz, *Jahresb. für Chem.* 1865, S. 360.

¹⁹ The reason, probably, is that the hydantoin combines more readily with the biuret in its nascent state, that is, as condensation of urea takes place, than with biuret fully formed.

²⁰ Strecker-Wislicenus, *Org. Chemistry*, London, 1881, p. 539.

Hydantoin is easily soluble, and so would pass on in the circulation to be combined elsewhere with two molecules of urea or with biuret, which is also soluble, to form ammonium urate.²²

It may be urged, as an objection, that in order to produce hydantoinic acid and biuret out of the body a temperature of 160° C. is required, and therefore that the body at the normal temperature of 37°–38° C. cannot produce this result. The fact that the conjugation of benzoic acid and glycocine takes place in the body at the normal temperature, when benzoic acid is introduced into the alimentary canal, hippuric acid being formed and passing off in the urine, to effect which conjugation out of the body requires exactly the same temperature of 160° C., is a complete answer to such an argument. But I will show directly that the combination of urea, or its antecedent ammonium cyanate, with other bodies does actually take place in the animal body.

Horbaczewski, in his paper in the *Monatshefte*, also describes a method for obtaining methyl uric acid by synthesis. He says:

"It was naturally to be expected, that if in the previous experiment, instead of glycocholl, a derivative of glycocholl was employed, instead of uric acid a derivative of uric acid would be obtained. The experiment was performed with sarcosine, and confirmed this supposition. When sarcosine is heated in small portions (0.1–0.2 gm.) with 5 to 10 parts of urea, after the method described for uric acid, and carefully warmed until the mass becomes solidified whilst hot—which can always be effected in the present case—the residue is found to contain methyl-uric acid. This can be demonstrated at once in the residue by the murexide test; in fact a small atom generally gives a much more decided reaction than can be obtained from the uric acid residue. If the experiment has been successful, the reaction is very striking. The methyl-uric acid can be separated from the residue in exactly the same way as described for uric acid. The purification of this compound can be effected far more easily than that of the uric acid, and presents no difficulties whatever."

The changes which have taken place here are, I venture to suggest, of the same character as those indicated for the formation of uric acid. The sarcosine is combined first with one molecule of urea, forming methyl-hydantoinic acid, which dehydrated into methyl-hydantoin, and then, combined with biuret, forms ammonium urate.

Now methyl-hydantoin has been actually formed after the administration of sarcosine to a living animal, and detected in the urine. Considerable discussion took place at the time this was announced, as to whether or not methyl-hydantoin really appeared in the urine, and a number of experiments were made by Schultzen, etc. The importance attached to the question at the time arose from the fact, that it appeared to demonstrate the existence of carbamic acid in the animal system, and to show that this acid was the immediate

precursor of urea. A good deal may be advanced in favour of this view of the formation of urea, but, as I have endeavoured to show that the antecedent of urea is ammonium cyanate, and as methyl-hydantoin has been formed by mixing together sarcosine, potassium cyanate, and ammonium sulphate, and digesting them at the temperature of the body (40° C.), the experiment with sarcosine possesses great interest and significance with regard to the steps by which uric acid is formed in the animal economy. In the *Zeitschrift für physiologische Chemie*, Dr. J. Schiffer gives an excellent summary of the experiments and views of the others, together with an account of his own observations and experiments. From this paper²³ I take the following extracts.

"Few investigations in the range of physiological chemistry have in recent times excited so much attention as those of Schultzen on the transformation of sarcosine in the animal body. In conjunction with Leon v. Nenki (*Zeitsch. für Biologie*, Band viii), he had previously found, on giving glycocine as food, the amount of urea excreted corresponded with the amount of N given. He repeated his experiments with methyl-glycocine or sarcosine. Increased secretion of urea did not take place; on the contrary, two new bodies appeared in the urine, both having an analogous composition, the one compounded of sarcosine and carbamic acid, the other of sarcosine and sulphamic acid. The first of these bodies was identical in its constitution with methyl-hydantoinic acid, but was not recognised as such by Schultzen. He concluded from his investigation that the sarcosine attached to itself the carbamic acid resulting from disintegration of the albuminous bodies, and which, in a normal condition, gives rise to the production of urea. With this hypothesis, it appeared very plausible that urea should disappear from urine containing sarcosine. He imagined, therefore, he had explained the mode in which urea was formed, and had thus solved one of the most important questions in physiological chemistry by the convincing proof of a carefully devised experiment."

"Salkowski found, after administering taurine, its uramido-acid, tauro-carbamic acid, in the urine (*Berichte*, vi, s. 744)."

"Later, E. Bauman and Hoppe-Seyler (*Berichte*, Band vii, s. 34) succeeded in forming methyl-hydantoinic acid synthetically under such conditions as might exist in the animal body. Equivalent amounts of sarcosine, potassium cyanate, and ammonium sulphate, were digested at a temperature of 104° Fahr., the potassium sulphate removed by alcohol, and the baryta salt of the acid referred to obtained."

"In a similar manner, Salkowski (*Berichte*, vii, s. 116) at the same time produced this acid, or rather, as it is easily decomposed, its anhydride, methyl-hydantoin."

"So far, everything seemed to confirm Schultzen's experiments; but, when further experiments were made, essentially different results were obtained. These experiments were undertaken by E. Salkowski on the one hand and Baumann and v. Mering on the other. The results obtained by all completely demonstrate the absence of sarcosine sulphamic acid. As regards methyl hydantoinic acid, Salkowski (*Berichte*, Band viii, s. 115) first stated, in the urine of dogs, it appeared only in small quantity after the administration of sarcosine; whereas Baumann and v. Mering, in their experiments on the human subject, showed that, after administering as much as twenty-five grammes of sarcosine, methyl-hydantoinic acid was entirely absent from the urine; and that Schultzen, in his experiments, could not have had this substance to deal with. At the same time, they discovered a probable source of error in his experiments—namely, that, in the presence of sarcosine, Liebig's test for urea fails. They discovered also, as Salkowski also did, that a portion of the sarcosine appeared unchanged in the urine. In later communications, Salkowski confirmed the view of Baumann and von Mering that, after the administration of sarcosine, there is no appearance whatever of methyl-hydantoinic acid in the urine."

"There appeared to be very little left then from Schultzen's experiments. One point only still remained for investigation. As the uramido-acids are so easily converted into their anhydrides, and as this is specially so in the case of methyl-hydantoinic acid and its conversion into methyl-hydantoin, this latter substance might possibly exist in the urine after the internal administration of sarcosine. Salkowski has given great care and attention to this point—without, however, arriving at any definite proof."

"This, then, was the state of the question when Professor Baumann informed me that methyl-hydantoin reduces sulphate of copper in an alkaline solution, and asked me to make some fresh experiments with sarcosine founded upon this reaction."

Schiffer then describes the experiments which he performed to de-

²² In the paper published two years ago, I suggested that the synthesis might take place also, in another way, by the conjugation of glycocine first with biuret, which, afterwards combining with urea, would form ammonium urate, but this would give a different molecular arrangement for uric acid, and the actual production of uric acid from hydantoin and biuret shows that the latter is the correct interpretation.

²³ *Zeitschrift für physiol. Chemie*, Bd. v, s. 267.

monstrate the existence of methyl-hydantoin in the urine, and thus sums up the result of his investigations.

"Our knowledge, therefore, of the destination of sarcosine in the organism may be formulated as follows. By far the greatest part is excreted unchanged; a smaller portion, one-fifth to one-sixth, is transformed into the uramido-acid we have been discussing, or rather into its anhydride (methyl-hydantoin), and a smaller portion is oxidised into methyl urea."

Sarcosine, then, undergoes little change in passing through the system, but a portion is converted into methyl-hydantoin. If, therefore, when glycocine is absorbed from the alimentary canal, it does not undergo the normal change, we may reasonably suppose that, when brought in contact with ammonium cyanate, it will be acted upon in the same way as sarcosine, and a portion transformed into hydantoin, and thus we have the first step towards the formation of uric acid. Circulating in the system, the hydantoin may, under certain conditions, so affect the central nervous system, and thereby the innervation of the kidneys, that, when it arrives at these organs, condensation of two molecules of ammonium cyanate may take place with elimination of ammonia, forming biuret, and thus be conjugated with hydantoin; or this condensation may take place independently of the nervous system. Condensation of the cyanates readily takes place, as is shown by the action of acetic acid on potassium cyanate, forming potassium cyanurate and potassium acetate.

Such a view, I think, meets all the difficulties which have been raised with regard to previous theories as to the formation of uric acid—difficulties which have been very clearly set forth by Dr. Garrod, in his Lumsian Lectures. Nor is it difficult to understand that if, as I have endeavoured to prove, the final conjugation of two soluble bodies takes place in the kidney forming the very slightly soluble ammonium urate (1—2400), a portion may not be excreted, but remain in the blood—overflow, as it were, and so pass on into the circulation; a result which certainly happens when the ureters are ligatured. The ammonium salt would then, meeting with the soda in the blood, be converted into sodium urate, the form in which it is deposited about gouty joints.

The appearance, then, of uric acid in the secretion is the result primarily of the non-transformation or metabolism of glycocine into urea—whether that glycocine be derived from the bile poured out into the duodenum, or formed elsewhere in the body.

I now come to the question of the abnormal formation of uric acid in the human system. Just as in diabetes, the essential fault lies in the inability of the system, either in the liver, or it may be elsewhere, to effect the metabolism of glucose, which then passes into the circulation and is discharged by the kidneys, so, in gout or gravel, the imperfect metabolism of glycocine is the primary and essential defect. Unchanged, it passes from the alimentary canal, or elsewhere, into the liver; there, under the action of the gland, it is conjugated with urea resulting from the metabolism of the other amido-bodies, leucine, etc., and is converted into hydantoin; it then passes on to the kidneys to be combined with other molecules of urea or biuret, forming ammonium urate, a portion of which overflows into the circulation, and is converted into sodium urate. It is not difficult to understand that, in persons who are addicted to the pleasures of the table, who are fond of port, and who take little exercise, the liver should become "sluggish;" that the gland-cells should, from overwork, become inactive or destroyed; or the terminations of the nerves should, from excessive stimulus, become somewhat paralysed, and the gland in some measure like the submaxillary after the injection of atropine. The result would be the imperfect performance of its function, and the non-metabolism of glycocine. But it is not every toper and gourmand who develops gout, nor is every gouty man necessarily a toper or a gourmand. Further, it is certain that uric acid is also present in excess in the blood under other pathological conditions which have no connection with arthritic mischief. How are these facts to be explained?

MEDICAL MAGISTRATES.—The Lord Chancellor for Ireland, on the recommendation of Viscount Monek, has appointed Dr. Lambert Hepenstal Ormsby, to the Commission of the Peace for the county Dublin.—Dr. Griffin, of Kilkee, county Clare, has been appointed a Justice of the Peace for that county.—Drs. Anderson and Weir have been appointed Justices of the Peace for the county Down.—Dr. Frederick H. Daly, of Amhurst Road, Hackney Downs, has been appointed a Justice of the Peace for the county of Middlesex, by the Lord Chancellor, on the recommendation of Lord Enfield, Lord Lieutenant of the county.

THE GULSTONIAN LECTURES, ON SPASM IN CHRONIC NERVE-DISEASE.

*Delivered at the Royal College of Physicians of London,
March, 1886.*

By SEYMOUR J. SHARKEY, M.B., F.R.C.P.,
Assistant-Physician and Joint-Lecturer on Pathology at St. Thomas's Hospital.

LECTURE III.

(Concluded from page 638.)

2. *Spasm produced in a Reflex Manner by Disease of Afferent Nerves.*—There is scarcely a more difficult subject in the whole range of nerve-pathology than that of reflex spasm. Cases of general convulsions, as well as of local spasm, are so frequently explained in this way, and are in so many instances quite insufficiently supported by scientific evidence, that one cannot help coming to the conclusion that many cases are accepted as of reflex origin, which, at any rate, carry very little conviction with them. Some reasons can be adduced for the difficulties which beset the diagnosis. Many of these cases occur where some sensory nerve is the seat of severe pain; or where a part is diseased which is painful to move. A good example of the former class is spasm of the muscles of the face, accompanying facial neuralgia; and, of the latter, rigidity in joint-disease. But the most ordinary method of expressing pain is, by some overaction of the facial muscles; while the ordinary way of preventing pain in joint-disease is by keeping the joint still, and opposing attempts at movement, by contraction of muscles which produce an opposite effect. This is so natural a contrivance, not only in man but in lower animals, that it must be looked upon as almost an involuntary act. Reflex muscular acts are in very different degrees capable of being controlled or modified by the will; and even if it be allowed that the latter plays a part in the limitation of the movements of a diseased joint, this does not prove that the act is not partly involuntary and reflex. In many cases, it is very difficult to form a definite conclusion with regard to this question.

No one who observes the great variety in the degree of reflex muscular contraction, produced by similar stimuli applied to different individuals, can be surprised at finding evidence that persistent spasm occasionally occurs as the product of a reflex act; or that a stimulus, which produces no motor result in one person, gives rise to definite muscular contractions in another, not equally healthy. Thus, in hemiplegia, accompanied by descending sclerosis in the lateral columns, deep reflexes are much more brisk than they were before the hemiplegia occurred; and contractures, Brissaud says, may be suddenly increased by comparatively slight injuries. If this increased reflex excitability be due to the hyperphysiological activity of the spinal centres, which have been loosed from cerebral control, similar disorders of nerve-centres rather than of nerve-fibres are probably the most fertile causes of reflex spasm. Hence, it is scarcely too much to say that the injury, or disease, which supplies the stimulus to the sensory nerve in such cases, though apparently the principal agent, is really so in many instances only from a particular point of view. That is to say, a mine exists in the patient which has been accidentally exploded by a stimulus applied to a nerve in connection with it; but, had the same nerve been connected with a healthy and stable centre, no spasm would have ensued.

In speaking, therefore, of the present division of the subject, namely, spasm produced in a reflex manner by disease of afferent nerves, we can scarcely deal with it apart from the next division, namely, spasm produced by disease of ganglionic cells. For it is questionable how far stimuli applied to afferent nerves in chronic disease would produce muscular spasm if the centres were healthy. I am not aware that there is evidence to show that gross or demonstrable disease of ganglionic cells produces spasm. But impalpable disorders do; such, for instance, as those resulting from their separation from the cerebral centres. Non-demonstrable disorders, however, are what we presume to be the basis of so-called functional spasms; and to these we shall revert presently.

Reflex spasm no doubt occurs, but how frequently it does so, or how far the afferent or efferent nerves, or the nerve-centres, take the leading part in its production, are points which can scarcely be estimated. As good an instance as I know of reflex spasm is recorded by Mr. Clutton