A CONTRIBUTION
TO THE THEORY OF THE
NERVOUS ORIGIN OF RHEUMATOID
ARTHRITIS.

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AMONGST those whose attention has been directed to diseases of the joints there is an impression, which is steadily gaining ground, that the disease which we know as rheumatoid arthritis, osteo-arthritis, or arthritis deformans, is in an especial manner associated with some lesion of the central nervous system.

This view, first advanced by the elder Remak and by Benedikt, was advocated by Senator in his masterly article in 'Ziemssen's Handbuch,' and has been placed upon a firmer basis by the researches of Dr. Ord, Sir Dyce Duckworth, Mr. McArdle, Dr. Latham, and Dr. Weber of New York.

The arguments which have been put forward in support of this theory may be divided into four classes :

First : Those based upon the clinical characters of the disease ; its causation ; the distribution of the articular lesions, and the absence of visceral complications.

Secondly: Those based upon various nervous phenomena associated with this disease, such as trophic changes in the muscles, bones and skin, the exaggeration of tendon-reflexes, painful muscular spasms, and the occasional occurrence of migraine and palpitation of the heart.

Thirdly: Arguments based upon the results of treatment, especially those obtained by some observers by the use of electricity.

Fourthly: Arguments based upon the similarity of the morbid changes observed in rheumatoid arthritis, to those resulting from joint affections more certainly of nervous origin.

Whilst reading the literature of rheumatoid arthritis it occurred to me that it would be interesting to examine some of these arguments in the light of a large number of observations, and I have collected a series of 500 cases, for the notes of which I am indebted to my father, Sir Alfred Garrod, upon which, as well as upon cases which have come under my own observation, are based the results which I propose to lay before the Society.

This series includes all the varieties of rheumatoid arthritis, from the non-articular disease of elderly people to the most extensive and general form of the complaint.

The points which I hope to bring out are the following:

First: That the causes of rheumatoid arthritis are such as might be expected to act upon the central nervous system.

Secondly: That the distribution of the joint lesions is such as would be likely to result from nerve lesions.

Thirdly: That the distribution of the lesions is similar to that of certain arthropathies of spinal origin.

The following case, which has recently been under my care, illustrates so many of the points to be discussed that I venture to give the notes in some detail.

A lady, æt. 46, with no hereditary tendency to joint disease, had always had good health until four years ago. At that time she spent six hours in a state of intense anxiety and excitement, and when her anxiety was relieved,

was seized with a violent hysterical attack, although she had never before shown any symptoms of hysteria. She was ill for some days afterwards, and four months later the joint trouble commenced. The catamenia, which had up to that time been perfectly regular, ceased at the same time. The joints of the feet were first affected, and almost simultaneously stiffness of the jaw was noticed; then the ankles, knees, hands, wrists, elbows, shoulders, and hips were successively attacked, the disease working up the limbs from the periphery.

The pain was at first confined to the affected joints, but afterwards was felt along the bones, and lately there have been attacks of intense spasmodic pain in the muscles around the right hip.

The deformity is extreme, and all the joints are limited in their range of movement. The hands are much distorted although the joints are hardly appreciably enlarged; the fingers are deflected to the ulnar side, and in the right hand the first phalanges are flexed upon the metacarpals, the second phalanges are extended upon the first, and the third are somewhat flexed upon the second, whilst in the left hand there is flexion of nearly all the joints. A sharp osteophyte upon the second knuckle of the right hand threatens to pierce the skin. There is much distortion of the toes and slight œdema of the legs.

The muscular wasting is most marked in the muscles of the hands and forearms. The finger-nails are dull, fibrous, and brittle, and the skin of the fingers is glossy and pink, but sensation is not impaired. The glossiness of the skin and the muscular wasting were noticed almost immediately after the joints of the hands became affected. There is no sign of any visceral disease; the heart's action is weak but there is no murmur. All the joints of the extremities being involved, I am unable to give any account of the tendon-jerks. The electrical reactions show nothing abnormal.

In the study of any form of joint disease the question

of the influence of heredity is one of extreme interest, but in the case of rheumatoid arthritis it is rendered very difficult by the vagueness of the notion entertained by the public on the subject of "rheumatic gout."

Sir Dyce Duckworth and Sir Alfred Garrod have expressed the opinion that the daughters of gouty parents are frequently attacked by rheumatoid arthritis, and the view of the former author, that the members of certain families are especially liable to fall victims of joint disease of whatever variety, does not appear to me to be in any way opposed to the nervous origin of rheumatoid arthritis, since we may readily suppose that the joints of those who inherit the arthritic diathesis would act as points of least resistance, and would become the seats of an arthritic process, as the result of disturbances of the nervous system insufficient to produce such changes in persons not so disposed.

For reasons above mentioned the following table, which contains the results obtained from the study of 500 cases, cannot claim more than an approximation to accuracy :

Family history of gout	64
„ „ doubtful gout	10
„ „ rheumatism	48
„ „ rheumatoid arthritis	11
„ „ hand-joint affection	14
„ „ joint affection	24
„ „ rheumatic gout	1
„ „ deformed joints	1
„ „ crippling by rheumatism	11
„ „ sciatica	2
„ „ gout and rheumatism	7
„ „ gout and hand affection	5
„ „ gout and crippling	2
„ „ gout and joint affection	1
„ „ gout and deformed joints	6
„ „ gout, rheumatism, and rheumatoid arthritis	1
„ „ rheumatism and joint affection	4

Family history of rheumatism and sciatica.	1
„ „ rheumatism and crippling	1
„ „ rheumatism and rheumatoid arthritis	1
„ „ rheumatism and hand affection	1
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	216

It will be seen that in 216 cases, or rather less than half, there was a family history of arthritic affections; of these gout holds the first place, being met with in nearly one fifth of the cases. Rheumatism occurs sixty-four times, but some of the conditions so named may very probably have been in reality rheumatoid arthritis. Of the remaining conditions, such as crippling by rheumatism, hand affection, deformed joints, &c., which may be grouped together as probably rheumatoid arthritis, there are eighty-four examples, placing this disease second to gout.

After allowance has been made for the fact that in any 500 people such family histories would frequently be met with, it still seems to me that it must be allowed that an arthritic tendency does play an important part in the causation of rheumatoid arthritis, and this conclusion is borne out by individual instances.

I have at present under observation a poor woman who presents a typical example of rheumatoid arthritis. Of her grandparents she knows nothing; her father and mother both had enlarged joints. She herself is one of fifteen children, six of whom grew up, and her three brothers and two sisters suffered from enlarged joints as she does.

In another case, that of a young woman, *æt.* 24, who is entirely crippled by the disease, I obtained the following history. Her father was rheumatic, her mother had a rheumatic affection of the knees, one brother died of rheumatic fever, and one sister had a rheumatic affection of the ankles.

I have not found that those patients in whom the dis-

ease begins early are more likely to have a family history of joint disease than those in which the first symptoms appear later in life.

The fact that only a part of the patients who have an arthritic family history inherit the actual disease from which they suffer, seems to me to be strongly in favour of the existence of a general arthritic diathesis.

To pass on to more immediate causes, no one who has read what Dr. Ord has written upon the subject can doubt that uterine disorders are among the most potent causes of rheumatoid arthritis, and their importance has been recognised by many other authors.

Of 176 cases in which the state of the menstrual function is noted, it was regularly performed in 105, and was irregular in period or in quantity in 71.

Of the women 267 were married and 144 single.

In 132 cases the extent of the family was noted, and of these 92 had less than six children, and 40 more. Two had thirteen, one fifteen, and one seventeen children and three miscarriages.

In five cases the disease was stated to have begun after a confinement, in three after a miscarriage, and in three during pregnancy; in two others the disease was worse after confinement, and in one during pregnancy, whilst one patient stated that she suffered less during pregnancy. Five gave a history of uterine or ovarian tumours.

The point which I am able to bring out most clearly is the influence of the menopause on the development of the disease, a fact to which Haygarth first drew attention. Eighteen patients dated its onset from a period within two years before the menopause, and forty-one from the two following years, and in five cases the two events were simultaneous.

The influence is, however, best illustrated by the following table and curve, which show the ages at the commencement of the disease of the male and female patients respectively.

Age at commencement.		Women.		Men.
0—9	...	3	...	0
10—19	...	18	...	4
20—24	...	21	...	3
25—29	...	33	...	7
30—34	...	33	...	10
35—39	...	37	...	5
40—44	...	51	...	5
45—49	...	57	...	8
50—54	...	51	...	12
55—59	...	37	...	10
60—64	...	29	...	10
65—69	...	23	...	10
70—80	...	2	...	3
80—90	...	1	...	0
Doubtful	...	15	...	2

It will be seen that in the female cases there is an unbroken rise till the five-year period 45—49 is reached, and afterwards an unbroken fall. In the male cases, on the other hand, there is no such regularity, the numbers tending to increase with age, with a rise between 20 and 30, a period mentioned by both Charcot and Lebert as one at which the disease is likely to begin.

The table shows moreover the far greater liability of women to the disease, the numbers being 411 women to 89 men.

The influence of worry and care in the causation of rheumatoid arthritis has been insisted upon by many writers, and it is adduced by Senator as an argument for the nervous origin of the disease. Such a history is seldom volunteered by the patients, and is often only to be elicited by careful inquiry.

I find, among the 500 cases, 34 in which such causes are mentioned, including bank failures, sick nursing and the like.

For the following instance I am also indebted to my father, but it is not one of those already mentioned.

A lady, aged between fifty and sixty, who had always enjoyed good health, lost her only daughter after eight or nine months' illness. The mother's grief was intense, and almost immediately after the daughter's death she was attacked by rheumatoid arthritis of both knees and the left elbow. In the course of a year or two her health was restored, but the affected joints were left perfectly stiff.

The influence of violent mental shock is most important from a theoretical point of view, and the cases related by Koht¹ have been repeatedly quoted. The patients were two men aged thirty-eight and twenty-six respectively, who developed well-marked rheumatoid arthritis soon after receiving intense shocks from the bursting of shells, one during the bombardment of Strasburg, the other during the Paris Revolution in 1848. Leyden² also states that in Strasburg many cases of this disease date their onset from shocks received during the siege of 1870.

It is at least possible that the illness of the lady above mentioned, in whom the disease began after a short period of intense anxiety, may be attributed to this cause.

¹ 'Berliner klin. Wochenschrift,' 1873, p. 304.

² 'Klinik der Rückenmarkskrankheiten,' p. 159.

In the series of cases there are two in which the commencement of the disease was preceded by a severe mental shock, the nature of which is not, however, specified.

The influence of accidents and injuries is most marked in the local variety of the disease, for most writers agree that chronic rheumatoid arthritis of the hip-joint usually follows an injury slight or severe.

In this connection the following case, for the notes of which I am indebted to Mr. Thomas Smith, is of interest.

The patient was thrown from his horse, which fell upon him, bruising his leg severely, and straining the hip. The accident occurred in South Africa. His medical attendant did not think seriously of the injury at the time. A month after the injury he sailed for England, and on his arrival was seen by Mr. Smith, who found much bruising of the adductor and other muscles but no sign of hip disease.

He recovered sufficiently completely to allow of his going out shooting nine months after the injury, and three months after that he hunted. Although walking a good deal he had to rest at times on account of his leg.

Two years and a quarter after the injury he began to suffer severely from the hip, but was able to ride for some time after this. The hip affection has steadily progressed, and he now presents a perfect example of chronic rheumatoid arthritis of the hip-joint.

The researches of Dr. Charcot, which show that injury to a joint is followed by dystrophy of the neighbouring structures, together with those of Berger, on the arthritis which follows fractures of bones, have been adduced as pointing to a close relation between the condition of the joints and that of the surrounding structures, so that injury to one may be followed by a reflex affection of the other. If this be so, it seems to me that we have here, at least a plausible explanation of the frequent occurrence of the local variety of rheumatoid arthritis after injuries of the neighbouring parts.

Nor are cases wanting in which the onset of general rheumatoid arthritis is attributed to an injury.

For example, a woman, æt. 30, whose right foot and hand and neck were affected, dated the commencement of the disease from an accident. In a man, æt. 45, whose hands, elbows, shoulders, feet, ankles, knees and neck were all affected, the disease began after a fall which caused a scalp wound and shock. In another case the disease invaded the fingers of the right hand after an injury to the fourth finger.

A similar case is recorded by Mr. McArdle, of Dublin.¹

Cold and damp have long been acknowledged as causes, but the cases in which I find this mentioned are only nine in number. One patient had lived in a damp part of Ireland; one had got wet and cold during a menstrual period; two attributed their troubles to sleeping in damp beds; two lived in damp houses before the disease began; two attributed the disease to exposure to cold, and one to drinking cold water when hot.

A case, quoted by Dr. Ord,² of a lady who sat for some hours, in evening dress, with her back near the wall of a damp marquee, also illustrates this point.

Dr. Charcot, in his thesis of 1853, laid great stress upon this cause, but he considered that the action of cold and damp must be prolonged, and that the symptoms not infrequently developed long after the removal of the cause.

In a certain number of cases there is a history of rheumatic fever, and this, as has been pointed out, probably accounts for most of the instances in which valvular disease is met with in association with rheumatoid arthritis. In some instances it is probable that an acute attack of rheumatoid arthritis has been mistaken for true rheumatism.

In the series of cases I find mention of previous attacks of rheumatic fever in eight. In four cases morbus cordis

¹ 'Dublin Journal of Med. Sci.,' 1885, i. 490.

² 'British Medical Journal,' Aug. 2nd, 1884.

is noted, and of these patients two had had rheumatic fever, and two, aged sixty-three and forty-six respectively, had aortic murmurs only.

Lastly, any depressant cause, such as a period of ill-health, overwork, or loss of blood, appears to be able to bring on the disease.

In his work on 'Diseases of the Nervous System,' Dr. Gowers mentions mental distress and anxiety, severe fright, exposure to wet, cold, and accidents such as spinal concussion or injury to one limb, as causes of progressive muscular atrophy. This resemblance between the causes of progressive muscular atrophy and those of rheumatoid arthritis is most interesting, for some observers have thought that spinal arthropathies result from lesions of the anterior horns of the grey matter, and arthropathies have been observed in connection with progressive muscular atrophy.

Leaving the subject of the causation, I will now pass on to speak of the distribution of the lesions in rheumatoid arthritis.

Dr. Senator¹ speaks of the symmetrical onset and progress of the disease as being hardly explicable, except upon the supposition of a central cause situated in the nervous system. That symmetry is one of the most marked characteristics of rheumatoid arthritis is a fact which is so generally recognised that it requires no proof. Sir James Paget and Dr. William Budd, in their papers on 'Symmetry in Disease' read before this Society many years ago, drew largely upon rheumatoid arthritis for their examples, and in some individual instances this peculiarity is extraordinarily well marked, as is shown by the following cases.

A man, æt. 32, had the middle joints of both index, ring, and middle fingers affected.

In a woman, æt. 64, the disease began in the middle joints of both middle fingers.

¹ Ziemssen's 'Handbuch der Speciellen Pathologie und Therapie,' Bd. xiii, S. 143.

A woman, æt. 49, had the end joints of the index, middle, and little fingers affected.

In a woman, æt. 36, the middle joint of the right middle finger was first attacked, and then the corresponding joint of the left hand.

A woman, æt. 52, had the knuckles of both index and middle fingers affected, as well as the metacarpo-phalangeal and interphalangeal joints of both thumbs.

A man, æt. 49, had the end joints of the index, middle, and little fingers attacked.

It is a curious fact that the joints of the ring finger appear to enjoy greater immunity than those of the other fingers. My father tells me that he has also noticed this.

Frequently the corresponding joints are not simultaneously attacked, but it is the exception to find a joint remaining long unaffected when the corresponding joint has become diseased, unless the case be a monarticular one.

In a considerable number of cases all the joints of one side of the body are worse than those on the other, and in rare instances, as the following, the disease is entirely unilateral. A woman, æt. 42, had the right elbow, right knee, right side of the neck, and right temporo-maxillary joint affected.

In some such cases Dr. Ord has found ovarian tenderness on the corresponding side.

Dr. Charcot has stated that the disease usually tends to spread from the periphery towards the trunk. That there is such a tendency I am convinced, but this point is much more difficult to demonstrate than the preceding, and in many instances there is certainly no such definite order of progression.

In the case of the lady mentioned at the beginning of this paper the order of the invasion of the joints accorded entirely with this view, the feet, knees, hands, elbows, shoulders, and hips being attacked in succession.

In order to ascertain the usual mode of progression of the disease, I have constructed a table showing the

number of times that each joint was attacked in the series of 500 cases. As the series contains cases in all stages of the disease, the order of frequency should correspond to the order of invasion; since the joints which are usually attacked late will, as a rule, be affected in advanced cases only, whereas those which are attacked early will be more frequently affected.

Joints affected.	Total.	Percentage.
Hands	430	86
Knees	303	60·6
Feet	172	34·4
Ankles	137	27·4
Wrists	133	26·6
Shoulders . . .	125	25
Elbows	125	25
Hips	73	14·6
Temporo-maxillary .	125	25
Neck	178	35·6
Back	15	3·0
Sterno-clavicular . .	2	0·4

The involvement of shoulders and elbows is equal, so that with the notable exception of the knees, this table shows a tendency of the disease to advance up the limbs from the periphery.

That there is no element of chance in the position of knee implication in the table is shown by the fact that it occupies the same position in each hundred cases considered separately.

	I.	II.	III.	IV.	V.
Hands	86	85	85	86	88
Knees	68	65	59	55	68

In 252, or rather more than half the cases, the disease began in the hands, in 64 in the knees, in 28 in the feet, so the knees must be regarded as especially subject to rheumatoid arthritis.

In the case of the neck and jaw the affection usually

amounted to stiffness only, but although the liability to jaw affection and spondylitis has been long recognised, and has been especially insisted upon by Sir Alfred Garrod, I think that the above statistics throw a new light upon the frequency of their occurrence.

When the male and female cases are separated the order of frequency is somewhat modified, owing to the greater frequency of monarticular cases among men.

With a view to the comparison of the distribution of the joint lesions with that of nervous arthropathies, I have collected some cases of the latter. Such cases are, however, with the exception of the arthropathies of *tabes dorsalis*, few and scattered.

It is well known that in *tabes* the joints attacked are usually one or two of the larger ones, and this agrees on the whole with what is found in the case of other more or less local spinal lesions. On the other hand, in cases diagnosed as concussion of the spine, the arthropathies, when they occur, tend to be distributed very much in the same way as the lesions of rheumatoid arthritis. This is what we should expect, seeing that in concussion of the spine we have a cause more nearly approaching those which tend to produce rheumatoid arthritis than any other in connection with which arthropathies have been observed.

I have found four recorded cases of concussion of the spine followed by joint troubles.

The first of these was reported by Dr. J. K. Mitchell¹ in 1833. The patient was a medical man who was thrown from his carriage, alighting upon the back of his neck and shoulder; he was instantly paralysed, partly in the arms, wholly in the legs. On the following morning there was swelling, heat, and redness of the hands and wrists with much pain. The pain was always abated by remedies applied to the affected part of the spine, and aggravated by pressure or friction there. The patient had previously had rheumatism. He recovered.

¹ 'American Journal of Medical Science,' 1833, vol. xii, p. 360.

The second case, which was reported by Sir William Gull,¹ is that of a man, æt. 38, whose hands, feet, wrists, and ankles were affected. He had partial paraplegia and anæsthesia of the lower limbs, and the sphincters were weak. The joints were reddened as in gout. The joint affection lasted for months. Here, also, the diagnosis was concussion of the spine.

In the third case, which is reported by Mr. McArdle,² of Dublin, the patient, a man, æt. 60, who had no hereditary tendency to joint trouble, fell backwards on a flagged floor. Here the knees, hips, and ankles were affected. There was paraplegia affecting the lower extremities. The patient made a gradual but complete recovery.

The last case was recently reported by Mr. Wherry,³ of Cambridge. The patient was a man, æt. 34, who fell from a haystack and struck his left side. The diagnosis was "concussion of the spine?" When brought to the hospital he was in a semi-conscious condition but answered questions when roused, and it was some time before his mental powers were fully restored. In addition to the joint troubles there was sweating of the left side of the forehead and herpes over the left supraorbital nerve. The joint troubles began about a week after the accident, and the joints affected were the wrist, those of the first and second fingers, the ankles, and probably the hips and knees slightly.

Mr. Wherry states, "There was not any difference between the appearance of the joints and that which manifests itself in rheumatism or rheumatic gout." And, again, "The small joints, wrists and ankles, were most affected, the left wrist acutely." As in the three other cases the joints soon recovered completely under treatment directed to the spinal trouble.

I do not mean to imply that these cases are of the nature of acute rheumatoid arthritis, but merely to point out that

¹ Guy's Hospital Reports, 1858.

² 'Dublin Journal of Medical Science,' 1885, i, p. 490.

³ 'Lancet,' 1886, i, p. 643.

in such spinal lesions the distribution of the joint troubles resembles that met with in that disease, there being the same tendency to symmetry, and to the affection of the small peripheral joints.

Although in this paper I have covered but a small portion of the subject, I think that the statistics which have been brought forward tend, on the whole, to support some such view of the etiology of rheumatoid arthritis as has been suggested by Dr. Ord.

We may adopt, at least as a working hypothesis, the view that the cases which we include under that name are cases of trophic joint changes due to some disturbance of the central nervous system. That such disturbances may be produced by a variety of causes, directly by mental anxiety or shock, or by the action of damp, cold, or indirectly by uterine disorders or local injuries. Lastly, we may suppose that in those who inherit the arthritic diathesis such influences would more readily lead to the production of joint lesions than in those who have no such hereditary tendency.

We must of course look to morbid anatomy to play the chief part in the further elucidation of the problem, but the study of the clinical aspects of the disease is also of great importance.

I, at least, believe that the lines of argument above discussed are those which must be followed up if the nervous theory of rheumatoid arthritis is ever to be established upon a firm basis.

To the associated muscular and cutaneous dystrophies I attach but slight importance in this connection, believing them to be only secondary to the joint lesions.

Dr. Charcot has described cases in which trifling injuries to joints, followed by slight arthritis, have led, by reflex irritation as he believes, to wasting of the muscles of the limb, and increase of the tendon reflexes, and it has been my good fortune to see two such cases under his care at the Salpêtrière.

That muscular wasting may result from any form of

joint lesion has long been known, and in rheumatoid arthritis, in which disease we have the most chronic and persistent joint lesions of all, we should naturally expect to meet with secondary trophic changes in their most pronounced form.

The recent observations of MM. Pitres and Vaillard,¹ who have met with changes in the peripheral nerves in this disease, suggest that such changes may perhaps play an important part in the production of secondary nervous phenomena.

¹ 'Bull. de la Soc. Biolog.' July, 1886.

(For report of the discussion on this paper, see 'Proceedings of the Royal Medical and Chirurgical Society,' New Series, vol. ii, p. 311.)