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THE INFECTIOUS ORIGIN OF RHEUMATOID ARTHRITIS

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(1) Introductory and Historical.

Rheumatoid Arthritis, Arthritis Deformans, Chronic Rheumatic Arthritis, are among the names given to the disease which is the subject of this thesis. The number of the names testifies to the uncertainty and disagreement among authorities past and present as to what these synonyms should imply. It was only after many years of observation and discussion that Rheumatoid Arthritis was differentiated from gout on the one hand and from rheumatism on the other. That still further subdivisions will be made in Rheumatoid Arthritis is certain when bacteriologists have made an exhaustive study of the disease. Up to within recent years the basis of division has been a clinical one, and pathologists and bacteriologists have had little to say in the matter. While many examples of the latest stages of the disease have no doubt come under inspection on the post-mortem table, it is obvious that very few such examinations of lesions in the early stage can be made in a disease which is quite compatible with great longevity.

The imperfect recognition of the disease is evidenced by the fact that as late as 1850 cases of

Rheumatoid Arthritis were exhibited before the Medical Society of London as examples of luxation of the distal extremity of the great toe!¹ Heberden (1805) was one of the first to give a description of the clinical features of the disease. He described the chronic nature of the joint affections, and the great muscular weakness, the severity of which is quite out of proportion to the joint symptoms. Graves in 1843 noticed the rapidity of the pulse and the vaso-motor disturbances. Sir Alfred Garrod made a definite advance by showing that excess of uric acid present in gout is absent in Rheumatoid Arthritis. In 1876 Senator advocated the neural origin of Rheumatoid Arthritis, and was supported by Spender in 1889. In 1892 appeared the first suggestion of the infectious origin of the disease by Max Schüller. The infectious theory and the neural theory divide opinions at the present day. Towards the former view I have been led by the study of my own cases.

If it is difficult to define Rheumatoid Arthritis it would be well, nevertheless, to classify those conditions which are included under that name. Directly infectious arthritides, such as tubercular, it does not include, nor arthropathies of spinal origin such as those occurring in tabes but of those cases which it does comprise there are two great classes, namely:-

1. Llewellyn Jones Arth. Def. p.12.

(1) Osteo-arthritis or the hypertrophic form, in which the ends of the bones are enlarged, exemplified by malum coxae senilis and by cases with Heberden's nodes.

(2) The atrophic form, in which the disease begins in the synovial membrane and periarticular tissues, the initial hypertrophy of these structures being succeeded in the later stages by atrophy. Atrophy of muscle is a prominent feature, and, in the later stages, atrophy of bone also. This class may also be subdivided into acute and chronic types. The acute examples occur in young adults, exhibit vaso-motor and circulatory disturbances, and sometimes pyrexia. The chronic cases occur in older patients in whom the constitutional disturbances are not so prominent.

I do not suggest, however, that this is to be made a hard and fast division, for in some cases a lesion characteristic of Class I. is engrafted on to an otherwise typical example of Class II. Thus in my own series of cases Heberden's nodes are present in three examples of the atrophic type (Cases 2, 3, and 4.)¹

(II) Current Views as to the Pathology of Rheumatoid Arthritis.

As already stated there are two views at the present day as to the pathology of Rheumatoid

1. Summary of cases at end of thesis.

Arthritis, viz. the infectious and the neural. Allusion has also been made to the scantiness of post-mortem records. In a certain number of cases examined post-mortem lesions have been noticed in the spinal cord, among these being disappearance and atrophy of the cells of the anterior cornua, and atrophy of the anterior roots;¹ also degeneration of the nerves supplying the affected limbs.² These cases conformed to the type classified as Chronic Rheumatoid Arthritis.

The bacteriological evidence to hand is very conflicting. Schuller³ has detected organisms in the joints resembling diplococci in 150 out of 230 cases of the disease. Bannatyne⁴, Poynton and Paine,⁵ and Fayerweather⁶ are among those who have isolated organisms from affected joints. The cases in which Bannatyne found organisms were of the acute type with rise of temperature, vaso-motor disturbances, and pigmentary changes.

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1. Archives Cliniques de Bordeaux quoted by Llewellyn Jones.
2. Mott and Tredgold "Brain" 1902 quoted by Jones.
3. Verhandl Deutch "Gesch f.chir"1892 quoted by Jones.
4. Rheum Arth. 1896
5. Trans. Path. Soc. 1902.
6. American Journal of Med. Science 1905.

On the other hand no organisms have been found by equally good observers, such as McCrae and Painter of Boston. Bearing in mind, however, the diversity of types which are all classified under the term "Rheumatoid Arthritis," it is possible that when more bacteriological work has been done in the type in which Bannatyne was successful, viz. the acute type with vaso-motor disturbances, we shall be able to generalize with more confidence.

Those in favour of the neural theory point to the nervous factors which accompany and precede the disease. Mental shock and worry appear to be important factors in its initiation in some cases: during the progress of the disease neuralgic pains, tingling and cramps are frequently noticed by the patients, and the muscular atrophy may be extreme, and indeed may actually precede the appearance of any arthritic trouble. Dr. Latham, of Cambridge,¹ who is a strong advocate of the neural theory, points to the similarity of acute anterior poliomyelitis and Rheumatoid Arthritis as regards muscular wasting. The resemblance is, however, not a real one. Case 2 in my series presented very marked wasting of the interossei muscles of the hands, the muscles of the forearms, and the supra and infraspinati muscles. Nevertheless, as the patient's condition commenced to improve, these muscles began to recover their bulk

1. Pathology of Rheum. Arth. 1905

and tone, and at the present time they are equal to what they were before the disease occurred. The inference would seem to be that the nerve cells in the anterior horn supplying these muscles were not destroyed irrevocably, as in anterior poliomyelitis but that their nutrition was so depressed that they were unable to supply trophic influences to the muscles affected. Dr. Latham also mentions in support of his theory the arthropathies which sometimes occur in hemiplegia. What at first sight seems a strong argument in support of the neural theory is the success which has attended Dr. Latham's treatment by counter-irritation of the spine. In two of my own cases (1 and 7) this was tried without any benefit. These two cases belonged to the acute type with pyrexia and vaso-motor disturbances, so that here again it is possible that my two cases were not properly selected ones. The benefit which has resulted from spinal counter-irritation is explainable if Latham's cases had been complicated by chronic inflammation of the meninges of the cord. This condition has actually been found post-mortem on several occasions.¹

1. Jones. Arth.Def. p.99.

Stronger are the arguments for the infectious theory, among which may be mentioned:- the number of cases in which a focus of septic absorption is present, the fact that great improvement, and sometimes complete cure, may result when measures are taken to eradicate that focus: the fact that in some cases, especially in that form to which infants are subject, namely Still's disease, splenic and glandular enlargements are found: the bouts of pyrexia with vaso-motor phenomena, suggesting a fresh absorption of toxic products: the analogy of other infectious diseases which give rise to arthritic troubles. The pigmentation of the skin seen in Rheumatoid Arthritis finds a counterpart in the same condition when present in chronic constipation. The desquamation of the skin finds a parallel in that occurring after scarlet fever. The rapid pulse might be explained by toxines acting on the vagus nerve. In Case I. in my series increase in rapidity of pulse varied directly with exacerbations and remissions of the vaso-motor symptoms, suggesting a periodic discharge of toxines

into the circulation. The observed preponderance of female over male cases might be explained by the greater chance of septic absorption from the genito-urinary tract in the female sex. Another strong point in favour of the infectious theory is the fact that success has in some cases attended the injection of antistreptococcal serum.

(III) The Rôle of Infection.

"An infection may be defined as a morbid change produced in the body by bacteria, and a disease or a lesion is infectious or infective if it be thus produced."¹

The result of the growth of organisms in the body is the manufacture of toxines. To these toxines are due the baneful effects of the infection. Of the possible sites at which organisms may enter the body, and there manufacture their toxines, the chief are:-

- (1) The nose and throat including the tonsils.
- (2) The alimentary canal.
- (3) The genito-urinary tract.

1. Gibson Text Book of Medicine p 55.

Germane to the subject of this thesis are the examples of acute rheumatism and acute tenosynovitis following tonsillitis. Professor Osler goes so far as to say that there is always a primary infection of the tonsils to which the rheumatic fever is secondary. Dr. Tracey of Boston¹ has reported two cases of acute tenosynovitis following acute tonsillitis. Rhinologists have shown in recent years that diseases like asthma may be due to a septic infection of the nares, and improvement has followed the injection of appropriate vaccines. Caries of the teeth is now held responsible for many maladies, and several leading dentists hold that pyorrhoea alveolaris may be the cause of rheumatoid arthritis. Drs. Wirgmann and Watson Turner enumerate twelve cases in which the condition appeared in conjunction with Rheumatoid Arthritis. They believe that an infection consequent on oral sepsis "may be due to absorption via the intestines, or to local extension via the gum and bone,"² and Dr. Kenneth Goadby³ holds the same view. The latter authority has been successful in treating

1. Boston Med. and Surg. Journal July 1907.

2. Lancet Dec. 4, 1909.

3. Lancet Dec. 25, 1909.

pyorrhoea alveolaris by suitable vaccines, with relief of the arthritic symptoms.

Intestinal tract. As is well known the normal intestinal tract swarms with organisms, both aerobic and facultative aerobic. But when putrefaction is present there is a decrease in the aerobes and a corresponding increase in the anaerobes. That the products of intestinal putrefaction are highly toxic has been proved beyond all doubt. The object of the soured milk treatment is to disestablish these anaerobic organisms and to implant colonies of lactic acid bacilli in their place. Colon irrigation has also been tried with success.

(IV) Personal Observations.

From my own private practice I have been able within the last year to collect twelve cases of Rheumatoid Arthritis. Of these no less than eight cases (Nos. 1, 2, 4, 7, 8, 9, 10, and 12) had some co-existing malady which was in all likelihood the focus of septic absorption. Of these eight cases in three (Nos. 1, 7, and 8) the onset of the disease

was acute in character, in two (9 and 10) subacute. The rest had an insidious origin. By "acute" I mean that the joint symptoms rapidly showed themselves and were accompanied by a rise of temperature. The cases with an acute onset were young patients.

Vaso-motor. Further, in cases 1, 7, 8, 9, and 10, there were marked vaso-motor disturbances. These were most noticeable in Case I. But in all these cases there was contraction of the peripheral arteries and mottling of the skin of the extremities and face. Coldness of the extremities was also a marked feature. In Case I the patient used to talk about having "a cold attack." I had the opportunity of examining her during several of these attacks. The radial pulse was almost imperceptible, and its rate was usually between 120 and 140 beats per minute. The feet and hands were icy cold in spite of the application of hot water bottles. A further feature of interest in this case was that during the asphyxial attacks the patient had temporary obscuration of vision: a condition which has also been found to occur in similar cases investigated by Llewellyn Jones¹

¹ Arth. Def. p. 36.

who concludes that, as the result of arterial spasm, degenerative change has taken place in the periphery of the retina.*

Sweating and Oedema. Localized sweating and oedema were a further manifestation in these five cases (Nos. 1, 7, 8, 9, and 10). It has been suggested that in such cases the alternate asphyxia and congestion of the blood vessels are responsible for the oedema. As far as Case I. is concerned I have little doubt that this was so. The oedema was greater after the bouts of arterial spasm and relaxation. In this connection it is significant to remember the similarity between Raynaud's disease and Rheumatoid Arthritis as regards the associated gastric and intestinal symptoms in each.

Increased Pulse Rate. In cases 1 and 7, the pulse rate was rapid. In Case 1. it sometimes reached 140 beats per minute. Spender noted that 80 per cent of his cases showed rapidity of pulse, and he attributed this phenomenon to inhibition of the vagus Nerve.

* Prof. Osler notes that in Raynaud's disease a similar spasm of the retinal arteries may occur. (See Osler "Angina Pectoris" *Lancet* March 26 1910 under heading "arterial spasm")

Pyrexia. Pyrexia was noted in four of my cases (Nos. 1, 7, 8, and 12). Most marked was the pyrexia in Case 1., in which an elevated temperature was maintained for weeks at a time, varying between 100° and 103° F. Any fresh extension of the disease in these four cases was accompanied by a rise of temperature, with increase in severity of the vasomotor symptoms. In the remaining cases rise of temperature was not observed; though it is possible that in some of these cases there was some pyrexia which passed unnoticed.

Pigmentation. In Cases 2, 3, 4, and 9, pigmentation of the skin was present. In Case 4 this was very marked, and desquamation of the skin went on at the same time. In case 2, which resulted in complete cure, the pigmentation disappeared. In the remaining cases, which resisted treatment, it persisted.

Associated Diseases. In Cases 1, 2, 4, 7, 8, 9, 10, and 12, there was present some intercurrent disease, which was capable of constituting in each case a focus of septic infection. In Case 1, Mucous colitis was present. Five years before the commencement of the present illness the patient was sent to hospital for

bleeding from the bowel and the passage of mucus in the stools. This condition had continued up to the commencement of her present illness. On several occasions I examined the stools. Streaks of blood and mucus were present. I think the presence of blood makes it clear that there was in the bowel a site from which septic absorption could take place. That this condition had a connection with the joint symptoms was evidenced by the fact that these were much ameliorated when colon irrigation was commenced. A further and permanent benefit was secured by the aid of draughts of milk soured by lactic acid bacilli, which resulted in a considerable improvement in the condition of the stools. Similar success with lactic acid bacilli has been reported by Tubby and by Andrews and Hoke.¹

In Case 2. the disease was associated with chronic lead poisoning and pyorrhoea alveolaris. By occupation the patient was a plumber and tin-smith, and in his case the disease began insidiously. Constant neuralgic pains in various parts of the body preceded the joint swellings. Oedema of the feet was a marked feature. Before treatment was

1. Tubby: Arth. Def. Lancet. Dec. 26, 1908.

commenced the teeth were in a bad state. Septic processes were going on along the gum margin with pockets of pus, and a blue line was present on the gums. At the outset of treatment the worst of the teeth were removed, and steps were taken to cleanse the remaining ones. At the same time the patient was given small doses of potassium iodide and guaiacol, as recommended by Luff.¹ Up to that time no headway had been made in combating the disease, but, following on the above measures, a marked improvement resulted. The patient had been much crippled by the disease, but at the present time he is doing a full day's work. The swelling of the joints has subsided. There is now no oedema of the feet and pigmentation of the face has disappeared as have also the neuralgic pains. Luff is strongly of opinion that Rheumatoid Arthritis "is due to micro-organisms gaining access to the blood, in the majority of cases probably through some chronic catarrh of the alimentary tract, although invasion may occur through the nose, pharynx, or air-tubes. During their growth toxins are produced and discharged

1. Brit. Med Assoc. Aug. 2, 1907.

into the circulation, giving rise to the nervous symptoms of the disease and producing the local sweating and pigmentation associated with it."¹

It is highly probable that in Case 2 the disease originated through the patient constantly swallowing organisms which came from the pockets of pus situated round the teeth.

Case 4 was complicated by cystitis due to bacillus coli infection. In this case pigmentation and desquamation of the skin were marked features.

Case 7 showed a great resemblance to Case 1, both in the age of the patient and in the presence of vaso-motor and sensory disturbances, as well as of pyrexia. In both these cases, moreover, deformity of the joints was a much less conspicuous feature than the sensory and vaso-motor symptoms. In Case 7 persistent acne round the mouth was present.

Cases 8 and 9 had uterine sepsis as an inter-current disease. In Case 8 Rheumatoid Arthritis followed a miscarriage with slight sepsis on two occasions. In Case 9 a discharge from the womb was

1. Brit. Med. Assoc. Aug. 2. 1907.

present for some time before the onset of rheumatoid symptoms. Both cases were characterized by contraction of the blood vessels of the extremities with resulting coldness.

Case 10 was an example of Rheumatoid Arthritis preceded by gastric symptoms. In this case dyspepsia of some standing resulted in a gastric ulcer. The patient was a male aged 58. The gastric ulcer had existed for some weeks, and the patient was in a very cachectic and emaciated condition. About this time he was attacked by Rheumatoid Arthritis affecting the feet and knees with much oedema and muscular wasting. Complete cure resulted after the gastric condition was put right.

Case 12 was an example of Rheumatoid Arthritis complicated by gonorrhoeal reumatism and chronic Bright's disease. In this case it is interesting to note that the sterno-clavicular joints were attacked, which seems to be a feature of cases having an origin from the gonococcus¹. Some benefit was obtained by the injection of gonococcal vaccines.

1. Llewellyn Jones p. 164.

The remaining Cases, viz. 5, 6, and 11, were examples of osteo-arthritis. In Case 5 it took the form of Heberden's nodes. Case 6 was a typical example of malum coxae senilis. Arterio-sclerosis was also present, and the patient has since had a hemiplegia due to cerebral hoemorrhage. In Case 11 there were Heberden's nodes and fluid in one elbow joint due to irritation by osteophytes. In these three cases there was a complete absence of the vaso-motor, sensory, circulatory, and cachectic features so conspicuous in the foregoing cases. Nor was there found in any of these cases a focus of sepsis.

(V) Summary of Conclusions.

Bacteriological research in Rheumatoid Arthritis has not proved the direct infection of joints by micro-organisms, but my opinion, based on the results of personal observations, is that the disease is caused by toxines produced at a site remote from the joints. I have shown that out of twelve cases, taken in the order in which they presented themselves to me, no less than eight were

suffering from Rheumatoid Arthritis plus some septic process. Five of these cases exhibited vasomotor symptoms, localized sweatings and oedema. Two exhibited increased pulse rate, and four pyrexia. Now these symptoms may be said to be characteristic of almost any chronic infectious disease. It is to the joint lesions that attention has usually been directed in Rheumatoid Arthritis. Little has been said in text books about the chronic cachexia accompanying it, or about the collateral features which it displays which are common to it and to infectious diseases in general. It has been pointed out that in Case 1 the patient suffered from a chronic lesion of the bowel for five years before the onset of joint symptoms. She was a constant sufferer from sore throats and from general debility during that period. Here we have evidence of a cumulative poison at work in the system. Similarly the patient in Case 2 had a premonitory period during which neuralgic pains were a prominent feature. It has also been shown that in two cases (1 and 7) the joint lesions were not so marked as the constitutional symptoms.

It may be asked: How are the joint lesions brought about? The answer is that they are most

probably due to the selective action of the toxins on the joint structures. Their action on the central nervous system is shown by the associated circulatory, vaso-motor, and sensory phenomena.

That the nervous system suffers first from the action of the toxins is shown by the constitutional symptoms of the premonitory period.

The beneficial results of treatment directed to counteract septic processes is a very strong point in favour of the infectious origin of Rheumatoid Arthritis.

Three of my cases (5, 6, and 11) were examples of osteo-arthritis. In these three cases no focus of sepsis was present, and the constitutional disturbances characteristic of the others were absent. Most competent authorities now regard osteo-arthritis as a class by itself, though it is admitted that symptoms of osteo-arthritis may be grafted on to a case of the atrophic type. This I have seen in three of my own cases (Cases 2, 3, and 4). No infectious origin is claimed for osteo-arthritis, and none was found in the examples of it that came under my notice.

p.	Age	Sex	Onset	Joints affected	pyrexial	vaso motor	cutaneous	Associated Disease
	16	Female	acute, premonitory period of ill health	Both knees, ankles (neuralgic pains in legs and wrists.)	Yes	Oedema of feet and ankles. Mottling of extremities Sweating. (Dilatation of pupil) Contraction of arteries	No pigmentation.	Mucous colitis with presence of blood in stools.
	50	Male	Gradual. neuralgic pains	Ankles, knees, finger joints, (Heberden's nodes) (ulnar deviation of fingers) (generalized neuralgia)	No	Oedema of feet and ankles	Pigmentation of left side of forehead	Pyorrhoea alveolaris, chronic lead poisoning.
8	72	Female	Gradual	Knees, wrists, ankles, shoulders. (Heberden's nodes) Ulnar deviation of fingers	No		Spots of pigmentation.	
4	75	Female	Gradual	Wrists, elbows, shoulders (Heberden's nodes) (Ulnar deviation of fingers)	No		Pigmentation and desquamation all over body	Bacillus coli cystitis
5	76	Male	Gradual	Wrists, knuckles (Heberden's nodes)	No			Gout

