Section of Odontology.

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The Experimental Production of Arthritis.

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If, clinically, removal of areas of sepsis round the teeth will cure arthritis, and if recovery is assisted by the injection of vaccines prepared from microorganisms recovered from those septic areas, then to prove completely the causation of arthritis by oral sepsis, these organisms should cause arthritis when inoculated into animals by oral routes. That is the proposition, the validity of which I set out to examine. No one has yet successfully defined those various changes taking place in and around joints which, for lack of a better word, I have called, collectively, arthritis. The nearest approach to a successful classification appears to be that of Rose and Carless [17], which I have abstracted as follows:

(1) Rheumatic Synovitis.—Causation, pyococcal. (a) Occurring in the course of acute rheumatism, involving one joint after another, usually followed by resolution or by thickened ligaments and loss of mobility. If in one joint only, this may be disorganized without suppuration, being then acute rheumatic arthritis. (b) Occurring as a chronic disease characterized by swelling of joints, caused by effusion into them; thickened synovial membranes and thickened capsular and other ligaments. May end in fixation by adhesions; no lipping of cartilage or bone changes, usually accompanied by chorea, erythema, or Osler's nodes.

(2) Osteo-arthritis (having various synonyms such as chronic rheumatoid arthritis, arthritis deformans, &c.).—Cause, auto-intoxication. Pathological changes are thickened vascular synovial membranes, proliferation of villi; cartilages showing fibrillation, multiplication of their cells, softening and wear. Later there is hyperplasia of cartilage into which ossification takes place producing lipping, the osteophytes (which may cause locking) occurring in the terminal stage. The exposed bone is sclerosed and eburnated, the below surface being more cancellous than normal. The disease is divided into three groups: (a) Chronic mono-articular; (b) chronic polyarticular, in which the characteristic finger symptoms are seen; (c) acute polyarticular, commencing with febrile attacks, steadily progressing unfavourably, the small joints being affected symmetrically.

Osler [14] deals mainly with arthritis deformans, does not attempt a real classification, leaves the etiology doubtful but probably of a chronic infective nature. He states that the changes are as above.

Adami [6] divides arthritis into the following groups: (1) Serous arthritis,
(2) sero-fibrinous arthritis, (3) suppurative arthritis, (4) osteo-arthritis; involving mainly the synovial membranes and ending in ankylosis. He states the causation to be increasingly severe infections, saying that acute rheumatism is of streptococcal origin.

Poynton and Paine [1] were the first to show experimentally the infectivity of acute rheumatism.

Beattie [2, 3], with Yates [4], &c., has published much work, showing plainly and in a straightforward fashion that streptococci cultured from cases of acute human rheumatism caused arthritis in rabbits. They also demonstrated the phenomena of relapsing experimental arthritis, and between 1906 and 1914 published reports of some hundreds of cases, which conclusively proved their thesis.

About 1909, Dr. William Hunter [5a] pointed out from his clinical experience, that low grade infections derived from septic foci in the mouth caused anemia.

In 1914, Rosenow [8, 9] reported that he had produced experimentally, various lesions, among others, arthritis from streptococci of oral origin. In 1915 [11] he stated that streptococci from various diseases often had a most striking affinity for the organ or tissues from which they had been isolated, and in 1916 [12] published more work on elective localization, especially showing that streptococci isolated from an upper left molar had an elective affinity for teeth, dental nerves and muscles of animals.

In the Lancet of 1919, H. Warren Crowe [15] pointed out the importance of guarding against the fallacy that "because the vaccine of a given organism has a pronounced effect on a patient, that, therefore, this organism must be the causal germ of the disease," and quoted Sir Almroth Wright's suggestion that vaccines were probably not nearly so specific as had hitherto been thought.

Kerr Pringle [16], in 1920, quoted Nathan [16a], who laid down the very important axiom that once the micro-organism has entered the blood, its connexion with the portal of entry ceases; and that for this reason removal of the affected teeth (if they are really the site of the original focus which is not always certain) will prevent re-infection or recurrences; that such processes have absolutely no influence on the joint condition as it already exists, for the joint condition itself is a focal infection.

Willcox [19], in 1921, stated that in the large group of cases included under the term rheumatoid arthritis, arthritis deformans, &c., the cause is probably infection of non-specific origin.

Lastly, in the Dental Cosmos for last month (Feb., 1922), Nodine quotes a letter from Rosenow in which Rosenow states that he has produced heart and kidney lesions from infecting the teeth of dogs; no other details are given.

Dogs were chosen as suitable subjects for my work, for their habits and diet are very human, and their large canine teeth are readily accessible and of finished growth. Rodent incisors are obviously unsuitable; the pulp enlarges towards the apex; the tooth is of continuous growth and never of a decently workable size, although the rabbit has a very definite low resistance to streptococci generally. Owing to the expense it has not been possible to use as many dogs as one would like for this series of experiments recorded, as follows:—

The first dog, a small black and tan terrier, was anæsthetized. I have found that the best anesthetic is chloroform until the animal is under, after this the anesthetic is continued by intratracheal methods, using a Junker's bottle. I give one part of ether
to two parts of chloroform. The terrier had attached to its right upper canine a piece of Angle's thick retention wire. In order to get this wire into place it was found necessary to cut into the periodontal membrane below the cingulum, which is not well-marked in the canine tooth of a dog. In the pocket so formed, strain No. 12 (Warren Crowe's fully hemolytic) was inoculated, the whole culture on one nasgar slope being used and emulsified in one drop of broth. It was found that the dog managed to remove the wire sometime between the third and fourth days, but as a quite definite pocket had been formed on the buccal alveolar surface between the bone and periodontal membrane where the wire-ends had been twisted together, the wire was not replaced. The whole culture, No. 12, on one nasgar slope was again inoculated with the aid of a barb broach into this pocket on the eighteenth and nineteenth days. The dog got quite used to my examination of its mouth, and did not mind the two little movements involved in inoculation. On the thirty-second day after the first inoculation the dog was in as good health, if not better than, when we received it. This was confirmed by Mr. Trevor Matthews of the Veterinary Department of the University of Liverpool, who one day examined all the dogs.

No. 1 Airedale was inoculated as follows: With the assistance of a dental student, Mr. Findlay, who worked a foot engine, under full anæsthesia the top of the crown of the left lower canine was removed by grinding, the pulp extirpated and a fine plain broach passed right through the apex, the operation being conducted with rigid asepsis. Into the pulp chamber, strains No. 7, 8 and 9 of the streptococci were inoculated in a concentrated emulsion, in plain broth. The pulp canal was closed with gutta-percha. On the eleventh day, the gutta-percha was removed, the pulp cavity being found quite dry. A plain broach armed with cotton-wool which had been inoculated with the same strains was passed right down to the apex. The cotton-wool was left there and packed in with a blunt broach; and the pulp chamber then sealed as before. Next day, the twelfth since the first operation, on the gutta-percha being removed, a small quantity of almost white pus escaped. An attempt was made to obtain cultures from this, but as the dog swept his tongue over the surface of the tooth immediately before the material was picked up we (Professor Glynn and myself) could not be sure that the material would be uncontaminated, although we attempted to sterilize the surface by dry heat. The culture proved to be grossly contaminated with Bacillus proteus; we could not be certain that streptococci were present. On the thirteenth day this dog developed slight lameness in both hip-joints (the night of the twelfth to thirteenth day had been a cold one); on the twenty-first day it again was slightly lame in both hindquarters. This proved on both occasions to be a transient condition and may have been due to the weather. As the lameness was fairly pronounced on the twenty-first day the left lower jaw was X-rayed. In spite of the movement of the dog during the short exposure (three seconds), I ventured to make a diagnosis from the film that there was certainly no bone destruction of a gross nature around the lower left canine.

No. 2 Airedale was operated upon in the same way as No. 1, but in this case the pulp was opened on the tenth day, when an abundant and free flow of whitish pus became apparent. Again the teeth were dressed with cotton-wool inoculated with streptococci; on the eleventh day there was only a small amount of pus, more sticky in consistency. On this day an attempt was made to cultivate from the pus and from the dressing remaining from the tenth day, but again all cultures were contaminated, probably in removing them through the last eighth of an inch or so of the pulp chamber, which could not be guaranteed sterile. This dog was noticed to be slightly lame on the twentieth day and was declared to be so by Mr. Matthews. No. 2 Airedale was X-rayed together with the first Airedale, and although a most restless dog a radiograph was obtained. It apparently shows a patch of rarefying osteitis behind and below the left canine; this together with a very free flow of pus leads me to think that a septic area if not actually an abscess has been established. It was largely a matter of opinion as to whether the dog was lame or not.

The fourth dog, was inoculated as above with a concentrated emulsion of all the streptococci obtained. The dog had been observed to cough once or twice before
the operation. Immediately after the operation I noticed it was coughing badly; the cough disappeared entirely about the fourteenth day. On the seventh day the dog was distinctly off colour, being lame in its near hind leg. This was confirmed by Mr. Matthews. It was reinoculated; no pus was observed. On the eighth day the dog was lame in both hind and its off fore leg, and was still coughing.

The dogs have not been killed as I want to give them every opportunity either of recovering or of becoming seriously ill.

It was perhaps unnecessary for me to confirm the fact that arthritis could be produced in rabbits by inoculation with streptococci of certain definite strains. However, I did this in order to be assured that repeated subcultivation had not lowered the virulence of the strains which I obtained. The following are details of the positive results:

Rabbit No. 8 was inoculated with a full growth of Professor Beattie's Micrococcus rheumaticus (intraperitoneal route). Twenty-eight days later the rabbit had a definite and established arthritis; it moved slowly in its cage, objected either to the caretaker or myself handling it, and when placed on the floor used its fore-legs rather than its back-legs, just the reverse of what a normal rabbit does. It was therefore killed and a post-mortem performed, the results of which I will give later.

Rabbit No. 9, inoculated with Professor Beattie's Micrococcus rheumaticus C—a fatal human type. Several days afterwards I thought it had arthritis; on placing it on the floor it was noticed that it progressed vigorously but was not attempting to use its near hind leg which was kept in the air with a most peculiar jerking movement. This animal was therefore killed on the twenty-eighth day.

Rabbit No. 10 was inoculated with Professor Beattie's strain No. S7. This rabbit had been noticed to be becoming sluggish in its movements, and on the twenty-eighth day was very obviously ill and was killed with the other two. It had the most peculiar gait I have yet seen in a rabbit. It did not hop with its back-legs as a rabbit should do, but walked very stiffly and very slowly.

The other rabbits, into which were inoculated strains 5, 6, 7 and 11—15, have maintained fairly good health.

As I write this rabbit No. 11 is however apparently going under. (It had recovered by the fifty-fifth day.—A. L.) It is evident therefore that the strains I am using will cause arthritis. The post-mortem examination of rabbit No. 8 showed thick yellowish pus in the knee-joint of the near hind-leg; this was cultivated together with a scraping of the endothelium, and streptococci were recovered. The heart blood proved sterile; all other organs were normal. From rabbit No. 9 no streptococci could be recovered from the joints of the back-legs or heart blood, whether on account of faulty technique or because they were absent is unknown. From rabbit No.10 streptococci were recovered from both knee-joints, but not from the heart blood, the cultures being, so far as one could see, identical with those inoculated. There was a suggestion of recent kidney infarct. I had neither time nor opportunity to identify by "sugar" reactions these streptococci recovered from the knees.

All the cultures obtained from Professor Beattie and Dr. Warren Crowe were inoculated into mice. On the third day the mice inoculated with strains 4, 5, 7 and 6, 8, had a distinct disinclination to use their fore-feet; this passed off and although massive doses of the streptococci 7 and 8 were then given to those respective mice no effect has been observed from them. Strain No. 12 caused lameness of all limbs in one mouse about the eighth day after inoculation. In all cases the effects were transitory. In the other mice there was apparently no departure from the normal—none of the streptococci were fatal to mice; and Miss L. Digby, of this Department, informs me that her experience of streptococci, which I know to be very extensive, leads her to the conclusion that only 25 per cent. of the partially hæmolytic streptococci are pathogenic to mice.
I give a brief description of the streptococci used:—

Strain 4: Haemolytic on Warren Crowe's medium; slightly haemolytic on laboratory blood nasgar; obtained from case of oral sepsis-arthritis.

Strain 5: As above.

Strain 6: As above, but non-haemolytic.

Strain 7: Non-haemolytic, from the throat of a case of acute rheumatism, Professor Beattie's number SI35.

Strain 8: Non-haemolytic, Professor Beattie's Micrococcus rheumaticus from a fatal case of rheumatic fever.

Strain 9: Non-haemolytic, Professor Beattie's Micrococcus rheumaticus C from a fatal case of rheumatic fever.

Strain 10: Non-haemolytic, Professor Beattie's No. S7 from a case of acute rheumatism with chorea and septic throat.

Strain 11: Non-haemolytic, Professor Beattie's No. S1 from a case of acute rheumatism with chorea.

Strain 12: From Warren Crowe: very haemolytic on his medium, moderately haemolytic on laboratory blood nasgar (of oral origin).

Strain 13: As above, but apparently true viridans type (of oral origin).

Strain 14: As above, but non-haemolytic (of oral origin).

Strain 15: As above, but fully haemolytic (from sputum).

It is necessary to examine the results of these experiments before arriving at a conclusion. I am informed that muscular rheumatism is very common in dogs, whilst arthritis, of the chronic rheumatic synovitis type, or osteo-arthritis proper, is rare. Thus given that everything was in favour of the development of the disease, such as lowered resistance and unsuitable environment, the dog would not react like a human being to equal infection under similar conditions, for it appears to have a higher natural immunity. This view is supported by the fact that the inoculated material was exploded, as it were, at the apex of the dog's teeth, and in human beings experience leads to the view that the methods adopted would have caused grave local disease. This experimental inoculation has not occurred in those human cases in which arthritis exists: the infection if by way of the pulp, is probably very much smaller in amount and certainly far less virulent. We know that the peri-apical tissues, given fair chances, put up a good defence, by means of fibrous tissue barriers; and that the micro-organisms reside mainly on the inner or tooth side of the abscess wall; are very scanty, if present at all on the outside of the abscess, and usually are completely absent from the pus if that is collected with due precautions so as to prevent disturbance of the micro-organisms.

Contrast with this my attempted introduction of very large amounts of powerful streptococci into the peri-apical spaces of the dog's teeth. There must have been an immediate reaction locally sufficient to wall off, digest, or otherwise dispose of the organisms, even if few in number, and the reaction was apparently permanent, and scarcely susceptible to forcible later attempts at breaking it down—unless artificial immunity was established—which I consider very doubtful. At all events I did not confirm immunity reactions of any sort by blood counts or agglutination, &c.

The clinical results were very small in my opinion, and I might add, still smaller in the opinion of the animal caretaker, although the veterinary specialist considered that certainly in the fourth dog there was an unusual "action" as he called it. The contrast was very marked when a comparison was made with the "action" of the rabbits, especially on the day on which the bad cases were killed, which was very cold. It was not necessary to study these animals for any length of time, the attempt at anything more than one step was
obviously painful to them, whilst it was necessary in the case of all the dogs to watch them walking, running, and at rest, before an opinion was ventured—except in that of No. 4, who was rather obviously "off colour" for two days.

I did not feel myself justified in attempting to do all the various things that really were necessary. To take temperatures, weigh the animals, renew the inoculations daily, obtain blood for cell-counts and blood-cultures, would have been rather too much to inflict upon them, even in the interests of science: this is only possible if one establishes a proper animal hospital with nurses and so on.

The experiments may be assessed in the following way:—

*Animals.*—Not very susceptible species used.

*Organisms.*—From human sources, definitely arthritic: causing arthritis in rabbits.

*Dose.*—Very large in pulp canal.

*Number of Organisms at Peri-apex immediately after Operation.*—Certainly a few.

*Method of Infection.*—The repetition of the inoculation produced a slow and continuous infection with exacerbations—as often occurs in human beings.

*Clinical Results.*—Very small.

*Radiographic Results locally.*—Doubtful.

*Bacteriological Results.*—Almost negative.

These results may be applied to human conditions in this sense, that undue stress has been laid on "focal infection" as a potential or actual causal agent of arthritis. For it seems rational to believe that this disease, which is not excessively common, may arise from focal areas if the resistance of the whole organism is very greatly lowered, or if the focal areas are excessively large and numerous. Further, it seems probable that an established infection may be avirulent, but that infection with a second strain may cause a general flare-up out of all proportion to the amount of circulating organisms. But in the large majority of cases, an acute infection of the human peri-apex, leading to a chronic abscess, does not terminate as an arthritis. But should one or two small areas of osteitis around the teeth or in the jaws be demonstrated radiographically, such as Stanley Colyer has recently described [22], then in cases of arthritis the physician or surgeon must not omit a thorough and complete bacteriological examination.

**Summary.**

(1) Certain strains of "rheumatic" streptococci when inoculated intraperitoneally produced arthritis in rabbits, but only slight arthritis in mice.

(2) These strains inoculated by oral routes into dogs produced only very slight arthritis.

(3) Too great stress is laid on the production of arthritis in human beings by "focal infection in the mouth."

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REFERENCES.