OBSERVATIONS ON THE ASSOCIATION OF HAEMOLYTIC STREPTOCOCCAL INFECTION WITH ACUTE RHEUMATISM

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Since Haig-Brown[1] described the occurrence of cases of acute rheumatism in association with an epidemic of tonsillitis among the boys of Charterhouse much epidemiological evidence has accumulated in favour of the association of acute rheumatism with haemolytic streptococcal infections. Longstaff[2] had already shown from a study of the Registrar-General's returns that there was a close association between the incidence curves of puerperal fever, scarlet fever, and acute rheumatism, while Dudley,[3] in a study of the association of acute rheumatism with outbreaks of tonsillitis due to the haemolytic streptococcus among the boys on board the training establishment *Impregnable*, has shown that the annual attack rates per 1,000 were 397 for tonsillitis and 43.7 for rheumatic fever. Glover and Griffith[4] have reported similar outbreaks in public schools where, as in the case of the training ship, sleeping arrangements were ideal for the transmission of droplet infections. A full study of this aspect of the question is to be found in Glover's Milroy Lectures (1930).[5]

Interest in this association of the haemolytic streptococcus with acute rheumatism has been enhanced of late by the work of Coburn in New York and Collis, Sheldon, and Schlesinger in London. Coburn[6 7] showed that when children suffering from rheumatic fever were removed from New York to Porto Rico, not only was the haemolytic streptococcus persistently absent from swabs of the throat, but rheumatic relapses were unknown, and the children made uninterrupted recoveries. When the children returned to New York, however, haemolytic streptococci reappeared in the throat, and several rheumatic relapses occurred. Collis[8] and Sheldon[9] reported an epidemic of rheumatic relapses in a convalescent hospital for rheumatic children. Here the relapses were all preceded by tonsillar infections due to the haemolytic streptococcus. Further attention has been drawn to the subject by the work of Todd,[10] who has demonstrated the presence of a high titre of "anti-haemolysin" in the blood of patients suffering or convalescent from acute rheumatism.

Four Cases Encountered in Edinburgh

During an investigation into the aetiology of acute rheumatism that is at present being carried out in Edinburgh, four cases have been encountered which illustrate this association, and which, in view of its importance in relation to the aetiology of acute rheumatism, are now reported.

CASE I

A girl, aged 3 years 9 months, was admitted to the Royal Hospital for Sick Children, Edinburgh, on March 29th, 1932, with a history of weakness and twitching of the right arm and leg for one week. There was no history of headache, strabismus, delirium, or coma, and no family history of rheumatism. The only points of note were that she had had intermittent attacks of pain in the right ear since infancy, and four weeks before admission she had had a "slight cold." On admission she was a well-proportioned, well-nourished child, of average intelligence, but very emotional. There were marked choreic movements of the face, eyes, and all four limbs, more emphasized on the right side. Speech was considerably impaired, and she was unable to feed herself; both tonsils were slightly enlarged. Nothing abnormal was detected about the heart. The urine contained albumin, and, microscopically, a few red blood cells, but no casts. The following are notes on the progress of the case.

March 31st: Antipyrine, 5 grains three times a day. April 5th: Patient feeding herself; still considerable ataxia. April 11th: Faint, discrete, erythematous, and irritating rash on trunk, ? antipyrine rash; antipyrine stopped. April 13th: Temperature 100.2°; widespread erythematous rash affecting trunk, lower extremities, and upper extremities to lesser extent—closely set, bright red spots, fading on pressure, not quite so fine as typical scarlatiniform rash; face flushed; no sore throat. April 14th: Rash rapidly fading. April 19th: Well-marked "peeling" of the face. April 30th: Patient active and cheerful, with no noticeable ataxia; had lost 10 lb. in weight since the 14th; had also had impetigo, which responded to routine treatment.

May 1st: Temperature 102°, pulse 140; tonsils congested; high-pitched, blowing systolic murmur audible in the mitral area; sodium salicylate, 10 grains three times a day. May 2nd: Temperature 101.2°, pulse 132; systolic murmur more intense. May 3rd: Temperature 101.2°, pulse 136; haemolytic streptococci isolated from throat swab; reduplication of second sound in pulmonary area; sodium salicylate stopped. May 5th: Skin reaction to intradermal injection of extract of haemolytic streptococci positive; Dick reaction negative; haematuria present. May 7th: Haematuria diminishing; face puffy. May 9th: Preceding night restless; patient very breathless; at 6 p.m. she had an attack of vomiting, followed by cyanosis and a period of intense dyspnoea; during this attack the heart sounds were tumultuous and entirely masked by murmurs. May 10th: Temperature 100°, pulse 148; patient still breathless; apex beat in the sixth intercostal space, just external to the midclavicular line; no pericardial friction. May 16th: Patient immensely improved; no dyspnoea; temperature normal; no abnormal constituents of the urine; apex beat in the fifth intercostal space, medial to midclavicular line; systolic murmur in mitral area much less intense. May 25th: Tonsillectomy performed; tonsils enlarged and septic. May 29th: Further outbreak of impetigo on the face. On June 3rd the patient was discharged from hospital, her general condition being good. The systolic murmur was still present, but much reduced in intensity; there were no abnormal constituents of the urine.

This case demonstrates a majority of the phenomena to which invasion of the body by haemolytic streptococci can give rise. A patient admitted to hospital with chorea, a typical rheumatic manifestation, subsequently develops a rash which, to all intents and purposes, is a typical scarlatiniform eruption; this, in turn, is followed by an outbreak of impetigo contagiosa. Almost immediately afterwards signs of cardiac involvement appear, accompanied by tonsillitis, and a few days later the patient has developed an attack of acute nephritis. Examination of the throat swab reveals the presence of haemolytic streptococci; there is a positive reaction to the intradermal injection of an extract of haemolytic streptococci, and the Dick reaction is negative. A further point of interest is the history of a "cold" three weeks before the onset of choreic symptoms. Glover and Griffith[4] have shown that febricula and feverish colds are often a definite manifestation of haemolytic streptococcal infection. If it be assumed that this "cold" was such an infection, then the case is in the same category as those described by Collis[8] and Sheldon,[9] where rheumatic relapses were usually preceded by a tonsillitis of haemolytic streptococcal origin occurring one to three weeks before the rheumatic manifestations appeared.

CASE II

A boy, aged 15, was admitted to a surgical ward of the Royal Infirmary, Edinburgh, on March 12th, 1932, with a history that five years previously he had been in hospital for

several months on account of a "poisoned leg" following upon a cut on his foot. He was quite well after this until seven weeks before admission to hospital, when his right leg became very painful at the site of the old injury. The boy was found to be suffering from an acute osteomyelitis of the right tibia, which proved to be due to a haemolytic streptococcus. After operative treatment he made a good recovery. The case notes were as follows. On April 12th the patient was transferred to the Astley Ainslie Institution, a convalescent hospital. April 14th: Temperature 101.8°, pulse 120; scarlatiniform rash over whole body; no sore throat; foul discharge soaking through the elastoplast bandage; discharge contained *Staphylococcus aureus* and *albus*, and haemolytic streptococci. April 15th: Temperature 103.2°; rash fading. April 25th: Temperature 100°; pain in left wrist and hip; swelling on dorsum of hand; left border of heart 1/4 inch external to nipple line; mitral systolic murmur; salicylates administered and antistreptococcal serum. May 2nd: "Serum rash." May 6th: Pain in right hip. May 8th: Temperature 102°; heart enlarged; aortic systolic murmur. May 10th: Red patches on leg round wound; ? erysipelas. May 29th: Heart still enlarged; mitral and aortic systolic murmurs. June 2nd: Skin reactions to the intradermal injection of an extract of stock haemolytic streptococci and to an extract prepared from the culture of haemolytic streptococci isolated from his own wound both positive; Dick reaction negative; haemolytic streptococci isolated from throat swab. July 4th: Injections repeated; reactions still positive; Dick reaction negative; no haemolytic streptococci isolated from throat. July 22nd: Patient discharged, much improved; apex beat in nipple line in fifth interspace; mitral systolic murmur, and reduplicated second sound in pulmonary area.

Here again in one patient is practically the whole range of the clinical phenomena of infection with the *Streptococcus haemolyticus*. First the local infection, manifesting itself as acute osteomyelitis; then the generalized intoxication characterized by a scarlatiniform rash, followed by what some would regard as the allergic phase showing itself as acute rheumatism; and, finally, a localized invasive phase, characterized apparently by a mild attack of erysipelas. That the joint and cardiac involvement in April was a rheumatic manifestation is suggested by the prompt response to salicylate, and the subsequent progress of the condition.

CASE III

This patient, a girl aged 12, was admitted to the Ear, Nose, and Throat Department of the Royal Infirmary, Edinburgh, on March 16th, 1932, with the following history. There had been an intermittent discharge from the left ear since she was 5. At the end of February, 1932, she had been taken ill with "influenza," and on March 6th she had again complained of pain in this ear, which was followed by a discharge. Subsequently a discharge, unaccompanied by pain, appeared from the right ear. There had been no vomiting or giddiness. There was a history of tonsillectomy five years previously, but no history of rheumatism.

On admission the patient complained of pain in the left ear, which contained some pus. The tympanic membrane was bulging, and there was mastoid swelling and tenderness. Examination of the throat showed that a small piece of the right tonsil had been removed; the left tonsil was still entirely present. The tonsillar lymphatic glands were much enlarged, and there were large adenoids. The progress notes were as follows.

March 17th: Schwartze operation on left ear; sinus healthy; growth of haemolytic streptococci obtained from pus from antrum. March 29th: Adenoids removed. April 4th: Temperature 102.2°, pulse 120; profuse discharge from both ears. April 5th: Schwartze operation on right ear. April 6th: Temperature 103.4°, pulse 140; no rigors. April 7th: Left jugular ligation; haemolytic streptococci isolated on blood culture. April 11th: 10 c.cm. scarlatina streptococcus antitoxin intravenously and 10 c.cm. intramuscularly. April 12th: 10 c.cm. antitoxin intravenously. April 13th: 25 c.cm. antitoxin intravenously. May 13th: Patient transferred to the Astley Ainslie Institution; still some discharge from right mastoid wound. June 6th: Patient complained of pain in lumbar region on walking, which responded to rest in bed. June 10th: Again complained of pain in lumbar region, and was put back to bed; temperature 97°. June 11th: Temperature 99.6°; salicylate administered. June 16th: Temperature 98°; patient allowed to get up. June 23rd: salicylate stopped. July 13th: Operation wounds healed.

August 4th: Temperature 98°; throat inflamed and tonsils swollen; complained of sore throat; systolic murmur in mitral area audible for first time. August 5th: Temperature 102°. August 13th: Temperature 98°; patient allowed up; throat normal; mitral systolic murmur still present. September 13th: Tonsils again septic. October 21st: Patient transferred back to Royal Infirmary; still complaining of pain in back; tonsils septic. October 29th: Tonsillectomy performed. October 31st: Patient transferred back to Astley Ainslie Institution; throat clear. November 28th: No haemolytic streptococci isolated from throat swab; negative skin reaction to intradermal injection of extract of haemolytic streptococci. December 12th: No haemolytic streptococci isolated from throat swab; skin reaction to injection positive. December 23rd: Patient discharged; mitral systolic murmur still present.

In this case a definite haemolytic streptococcal infection was followed by what must be considered as a rheumatic infection of the heart. Not only was the haemolytic streptococcus isolated from the local infection, but it was also obtained on blood culture. There was no family history of acute rheumatism nor had the patient herself ever previously shown any signs of a rheumatic infection.

CASE IV

A woman, aged 26, whose first child was born on December 30th, 1931, was admitted to a fever hospital on January 7th, 1932, as a case of puerperal fever. She was discharged on March 1st. On April 2nd her temperature was 101°, and she complained of pains in the knees, thighs, arms, shoulders, and right iliac fossa; these responded to salicylate. She was admitted on April 22nd to the Gynaecological Department, Royal Infirmary, Edinburgh, on account of pain in the right iliac fossa. The tonsils were enlarged. A diagnosis of pyosalpinx was made, and she was discharged on this occasion on May 10th. For four weeks in August she was in bed at home with a recurrence of acute rheumatic polyarthritis.

On November 6th she was readmitted to the Royal Infirmary on account of persistent pain in the right iliac fossa, and of pain in the "small of the back" and on micturition. The joint pains still persisted to a slight degree. On admission there was a blowing systolic murmur of the heart, maximal in the mitral area. The tonsils were large and ragged. The case notes were as follows.

November 8th: Subtotal hysterectomy performed; haemolytic streptococci isolated from pus from pyosalpinx; pains improved considerably after the operation, and in addition salicylate was administered. December 3rd: Patient transferred to Astley Ainslie Institution. December 12th: Haemolytic streptococci isolated from throat swab; skin reaction to intradermal injection of extract of haemolytic streptococci strongly positive. January 4th, 1933: Haemolytic streptococci isolated from throat swab; skin reaction to injection strongly positive; patient receiving salicylate; joint pains easier. January 23rd: Haemolytic streptococci present in throat swab; skin reaction still strongly positive; patient getting up for a short time each day; pains now absent. February 6th: Haemolytic streptococci isolated from throat swab; skin reaction positive to injection; loud, blowing systolic murmur still present in the mitral area; patient now up all day.

In this case the haemolytic streptococcal infection took the form of an attack of puerperal fever, followed by a pyosalpinx, which, on bacteriological examination, was found to be due to this organism. Here again there was no previous history of acute rheumatism, nor any family history, and it was only after a haemolytic streptococcal infection that an initial attack of acute rheumatism occurred, leaving in its train a definite cardiac lesion.

Discussion

If it is assumed, as is indeed probable, that the " cold " reported in Case I was a haemolytic streptococcal infection, then in each of the cases the rheumatic manifestations were preceded by such an infection. Another feature of all four cases is the absence of a previous history of rheumatic infection and of any family history of this disease. On the other hand, there is much variation in the period intervening between the onset of the haemolytic streptococcal invasion and that of the rheumatic manifestations. In view of the clinical picture and the response of these cases to sodium salicylate, there can be little doubt that the cardiac and arthritic signs were of rheumatic origin.

It must be borne in mind, however, that this is not a random selection of cases. For every case here reported there were many more where either haemolytic streptococcal infection was present without associated rheumatism, or acute rheumatism existed without any evidence of haemolytic streptococci being involved, although the former was the more common finding. In other words, haemolytic streptococcal infection without any accompanying or consequent rheumatic manifestations was much more frequently found than acute rheumatism without some evidence of haemolytic streptococcal involvement. This is a factor which is of the greatest importance in any attempt to assess the role of the haemolytic streptococcus in the aetiology of acute rheumatism. It has been pointed out elsewhere[11] that if any series of cases of haemolytic streptococcal infection be examined the majority of cases of acute rheumatism in the series will be found to be secondary to such infection, whereas in a series of cases of acute rheumatism the number of cases secondary to haemolytic streptococcal infection will be much smaller.

The cases here reported are deliberately chosen because of the dominant part played by the haemolytic streptococcus, and in order to emphasize the important, though perhaps not primary, role of this organism in the aetiology of acute rheumatism, a role which must always be considered in any attempt to investigate the aetiology of this disease. That a close association does exist between the haemolytic streptococcus and acute rheumatism is exemplified even in this short series, where the latter condition was found in association with: (1) tonsillitis, (2) otitis media, (3) mastoiditis, (4) puerperal fever, (5) pyosalpinx, (6) acute nephritis, (7) acute osteomyelitis, (8) erysipelas, (9) impetigo, and (10) scarlet fever, in each case haemolytic streptococci being isolated as the causal organism. To argue from this, however, that the micro-organism is the primary cause of acute rheumatism is not valid, in view of the much larger number of cases in which no evidence of acute rheumatism is ever found.

The value of the cases in this series is further enhanced by reason of the fact that in none was there any family or previous history of acute rheumatism ; it is not possible to argue, therefore, that we are here dealing with the invasion of tissues already susceptible to the disease. Again, the period elapsing between the first signs of haemolytic streptococcal invasion and the onset of the rheumatic manifestations is so variable that it argues strongly against the haemolytic streptococcus being the primary cause of the disease.

As suggested elsewhere,[11] the present position would seem to be one of two alternatives: either that infection with the haemolytic streptococcus facilitates the invasion of the tissues by some specific agent, or that the haemolytic streptococcus may so alter the tissues susceptible to rheumatic infection as to prepare the way for invasion by this specific infective agent.

I have to acknowledge my great indebtedness to Lieut.-Colonel John Cunningham, superintendent of the Astley Ainslie Institution, not only for permission to study the cases under his charge and for full access to the case notes, but also for the sympathetic assistance which I received from him at all times. I am similarly indebted to Professor Charles McNeil for permission to publish the notes on Case 1. This work was part of a larger study of acute rheumatism which was being carried out in co-operation with Dr. H. J. Gibson of the department of bacteriology, and before my entrance to the Royal Navy, with the aid of personal and expenses grants from the Medical Research Council, and latterly during my tenure of the Davidson Research Fellowship in Bacteriology.

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MENTAL DEFICIENCY AND HEREDITY

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A little over a year ago I completed an investigation into the incidence and circumstances of retarded school children and mental defectives, which had for one of its objects the investigation of medical and family histories of all defectives of school age within a defined area. An attempt was made to estimate the relative importance of various factors in the causation of mental deficiency, and it is the purpose of this paper to give a brief account of this aspect of the original investigation. Other relevant matters are referred to from time to time, as appears necessary to the purpose in view. If in places this short contribution seems ragged, and poor in supporting evidence, indulgence is asked on the ground that it is the essence of a thesis some ten times its length, an important part of which was the presentation of genealogical charts which consideration of space precludes from reproduction here.

Introductory

The area referred to is the north-east quadrant of East Suffolk, with a total population of 45,435, a school population of 6,645, and a density of population of 0.3 persons per acre. The chief industries are agriculture and fishing. Communications across country are relatively poor, and many villages are still comparatively isolated. Social cohesiveness is high throughout the area, and remarkably complete family histories were obtained, as a rule, without great difficulty. The standards employed were those fully described by Dr. Lewis in his report.[1] A total of 750 children (11.2 per cent. of the entire school population) was examined by individual methods, and there is every reason to believe that the ascertainment of defectives was, for practical purposes, complete. Stanford tests and Burt's graded tests were used respectively in the estimation of mental and of educational age. The investigation of suspected defectives of school age followed closely that usually undertaken in the completion of Form 306 M. of the Board of Education ; that of suspected adults was made with the social concept of deficiency in mind. It was neither practicable nor indeed desirable to subject adults to systematic testing.

While it is clearly impracticable to submit any details of individual cases, it may be said generally that judge-