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History and importance of scrofula

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The clinical entity called scrofula has for many centuries, by its highly visible characteristics, provided a marker for tuberculosis.

In his book *A Handbook of Geographical and Historical Pathology*, August Hirsch[1] provided a picture of scrofula as it was understood until the discovery in 1882 of the tubercle bacillus by Robert Koch. The term scrofula, he stated, "denotes an inflammatory kind of tumour, more particularly in the neck". The word is a diminutive of the Latin word scrofa, a breeding sow supposedly prone to the disease, which was recorded by Aristotle.[2] The word corresponds etymologically to the Greek for pig, but Hirsch questioned whether it should not be taken in the figurative sense meaning a stone, reflecting the scirrhous hardness of the lymph glands when inflamed, as described by Galen. The word scrofula is first encountered in medical writings of the school of Salerno, Italy, in the early 16th century, but it first became a "technical term", as Hirsch puts it, in the Hippocratic period in Greece when the condition was especially common in children and its protracted course and "cold and mucous nature" were identified. The lack of knowledge about its microbial cause hampered final confirmation of its unity with other forms of tuberculosis until the end of the 19th century. Despite Koch's demonstration of tubercle bacilli in scrofulous lymph nodes, some writers remained unconvinced, either on epidemiological grounds or on the basis of human inoculation experiments, that scrofula was transmissible; this led them to deny a link with tuberculosis and thus to reject the unity of scrofula and pulmonary tuberculosis. Even William Osler, convinced as he was by the work of Koch, wrote "It is not yet definitely settled whether the virus which produced the chronic adenitis or scrofula differs from that which produced tuberculosis in other parts".[3]

In this account, we consider three aspects of the history of scrofula—the King's Evil, Marfan's law, and the place of this type of tuberculosis in the epidemiology of this disease.

King's Evil

It was widely believed for many centuries that the Royal Houses of England and France had a supernatural gift to cure scrofula by touching the sufferers (figure 1). Clovis of France (481-511) and Edward the Confessor (1042-66) of England were believed to be the first kings endowed with this particular gift.[4] In Macbeth (Act IV, Scene 3) Shakespeare gives a striking and accurate description of the ceremony of the royal touch (figure 2). Daniel[5] suggested that "royal claims of a cure might have gained widespread acceptance" because "tuberculosis adenitis usually represents primary infection with often a benign course and that primary infection often confers immunity".

The formal practice of the ceremonial rite can be traced back to the reigns of St Louis (Louis IX 1226-70) in France and Edward III (1327-77) in England. Edward III was the first English king to order a public display of this rite; he used a medallion called a touch-piece, which was given to sufferers as a sort of talisman.[6] Initially, the ceremony consisted of the king washing the diseased flesh with water, but Henry VII discontinued this practice. Instead, the ceremony consisted of the king touching the afflicted subject while the court chaplain recited prayers and presented the touch-piece, which was usually suspended by a silk ribbon around the neck. Edward I (1272-1307) touched 533 of his subjects in 1 month; Philip VI of Valois (1328-50) touched 1500 at a single ceremony; Charles II (1660-82) according to the registry, touched 92 102 people during his 22-year reign, at times 600 in one ceremony. Louis XVI, soon to meet the guillotine, was anointed at his coronation with the Holy Oil of Clovis on June 11, 1775, and "three days later in the summer, he ritually touched 2400 stinking sufferers from scrofula".[7] William III (1689-1702) allowed the ceremony to lapse after a single performance with the remark to the ailing people, "God give you better health and more sense". He refused to touch the patients but

Figure 1: **Queen Mary I touching the neck of a boy for the King's Evil (watercolour by M S Lapthom, 1911)**
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Enter a doctor

Malcolm Well; more anon—Comes the king forth, I pray you?

Doctor Ay, sir; there are a crew of wretched souls
That stay his cure; their malady convinces
The great assay of art; but at his touch—
Such sanctity hath heaven given his hand—
They presently amend.

Malcolm I thank you, doctor [*Exit Doctor*

Macduff What's the disease he means?

Malcolm 'Tis called the evil:
A most miraculous work in this good king;
Which often, since my here-remain in England,
I have seen him do. How he solicits heaven,
Himself best knows: but strangely-visited people,
All swoln, and ulcerous, pitiful to the eye,
The mere despair of surgery, he cures,
Hanging a golden stamp about their necks,
Put on with holy prayers; and 'tis spoken,
To the succeeding royalty he leaves
The healing benediction. With this strange virtue,
He hath a heavenly gift of prophecy,
And sundry blessings hang about his throne,
That speak him full of grace.

Figure 2: **Passage from Macbeth (Act IV, Scene 3) describing the ceremony to cure the King's Evil**

referred them to the exiled James II in France. The practice was continued by the exiled Stuarts and was frequently done in Italy by James Stuart, "the old pretender", and by his two sons, Charles and Henry (Cardinal of York). Samuel Johnson was one of the last sufferers of scrofula to be touched. As a child, he was taken to Queen Anne (1702–14). His step-daughter recalls that he wore his touch-piece proudly into adulthood along with the scars on his neck.[8]

Marfan remembered

In 1886, Bernard Jean Antonin Marfan (1858-1942) stated that individuals with scars from lupus and scrofula rarely develop phthisis (pulmonary tuberculosis).[9] This clinical observation came to be known as Marfan's law.

Support for Marfan's observation came from Von Pirquet[10] and Fowler.[11] Osler[3] doubted the validity of his law. The question of whether Marfan's law was true or false remained controversial for many decades until the work of Francis in Britain,[12] Magnus in Denmark,[13] and Sjögren and Sutherland in Sweden[14] revealed that pulmonary tuberculosis was less common in communities with a high prevalence of tuberculosis in cattle than in those with less bovine infection.

The bovine tubercle bacillus *Mycobacterium bovis* has been a common cause of cervical adenitis in human beings in countries with a high prevalence of tuberculosis in cattle. In England, for instance, as late as the 1940s and 1950s, *M bovis* was responsible for 57·5% of cases of cervical adenitis but for only 1-2% of cases of pulmonary tuberculosis.[15] Although the cause of the adenitis observed by Marfan is not known, it is reasonable to suppose that most of the cases were caused by the bovine strain in the light of subsequent epidemiological studies.

It is now clear that cervical adenitis may arise in two distinct ways. Cervical lymph nodes may be a part of the primary complex when the primary focus is located in the tonsils and pharynx, as happens in infection with bovine tubercle bacilli spread by contaminated milk. The alimentary route of infection may also lead to the glandular component of the primary complex in the mesenteric lymph nodes. Although human disease as a result of bovine infection is now rare, it may be serious and even fatal.

Cervical adenitis due to *M tuberculosis* is a feature of the spread of infection from the lungs, usually (or perhaps almost always) through the haematogenous route, though lymphatic pathways have been proposed.[16] This type of cervical adenitis is serious because it indicates that there are tuberculous foci in the lungs and that there may be other haematogenous foci in the body.

Cervical adenitis may also be due to non-tuberculous (environmental) mycobacteria, in most cases *M avium-intracellulare* or *M scrofulaceum*.[17] This illness occurs in children in areas where bovine infection has been eradicated and human tuberculosis has become rare and where appropriate environmental mycobacteria are prevalent.[18] In British Columbia, cervical adenitis due to atypical mycobacterial infections has become the most common form of mycobacterial adenitis in childhood.[19]

Epidemiological importance of cervical adenitis

Tuberculous lymphadenitis accounts for some 5% of total active cases of tuberculosis reported in Canada.[20] It is unevenly distributed in the population, being especially common in immigrants from Asia, in whom this form of disease accounts for about one-quarter of all active cases. In Canada, cervical adenitis is also more than twice as common among Indians and the Inuit than in the white Canadian-born population.[21] In all these groups, the disease is mainly caused by *M tuberculosis* with *M bovis* accounting only for about 1% of cases.[20]

In a study of tuberculosis in British Columbia among immigrants from five Asian countries between 1982 and 1985,[22] tuberculous adenitis accounted for 24% of total active cases, varying from 10% for those born in Japan to 44% for those born in the Philippines. The high frequency of cervical adenitis in immigrants from Asia has been found elsewhere. In the UK, a survey in 1971 by the British Tuberculosis and Thoracic Association showed that lymphadenitis accounted for 25·3% of all tuberculosis notifications in patients born in India and Pakistan.[23] The Scottish National Survey of tuberculosis notifications in 1993[24] confirmed a relatively high rate of non-pulmonary disease in immigrants from the Indian subcontinent (47%), with lymphatic disease making by far the largest contribution (67%).

Discussion

Tuberculous cervical adenitis has afflicted mankind probably for thousands of years. That royalty was believed to possess supernatural powers over this disease points to its frequency over the past 1500 years. However, a more serious study of all the historical documents relating to the royal touch might provide us with meaningful epidemiological data on this type of tuberculosis. By contrast, the occurrence of pulmonary tuberculosis was not often mentioned before the middle of the 15th century. Descriptions of phthisis by Hippocrates and by others from antiquity leave open the possibility that aetiologically different, yet clinically similar, wasting diseases were included under this title. Such considerations accord with Bates' and Stead's suggestion that the human tubercle bacillus has evolved only during the current millennium.[25]

Marfan's law was scarcely referred to by Marfan's contemporaries and has been largely forgotten, although the name of this astute French paediatrician is remembered by many medical students for the syndrome that he described. In many countries it took decades to show that cervical adenitis is often of bovine origin, and a similar period to show that infection with *M bovis*, acquired usually through contaminated milk, is protective against respiratory infection with the human tubercle bacillus. Perhaps the rapid and successful attempts to control and virtually eradicate bovine infection when the onslaught of infection with *M tuberculosis* had peaked was a mixed blessing: human infection with the bovine strain was an unintended and dangerous, yet potent, vaccination. In retrospect, it is not surprising that Marfan's law remained controversial for so long. Clinicians whose patients with cervical adenitis were predominantly infected by bovine bacilli were convinced of its truth, whereas those who dealt mainly with adenitis caused by the human bacillus were, like Osler,[3] rather doubtful.

Non-tuberculous mycobacteria seem to have replaced the bovine bacillus both as a cause of cervical adenitis[19] and as a natural vaccinating agent.[26] Infections with these organisms act as a rather weak vaccine with few complications in individuals with a normal immune response.

The reason for the high frequency of adenitis in immigrants from Asia is not completely clear; it is probably, at least partly, the expression of the tuberculosis epidemic in these groups at an earlier stage than that seen in Europeans. Lin,[27] in his thoughtful analysis of the tuberculosis problem in East Asia and the South Pacific area, suggested that the high frequency of extrapulmonary tuberculosis and of tuberculosis in children, and the almost equal incidence of tuberculosis in males and females are all suggestive of an earlier stage of the tuberculosis epidemic. Cummins, in his monograph *Primitive Tuberculosis*,[28] provides plenty of evidence of the high frequency of lymphadenitis in the early stages of the epidemic.

AIDS will open a new chapter in the story of scrofula. Not only can HIV itself cause lymphadenopathy, but also the loss of immunity allows for both the recrudescence of latent mycobacterial foci in the glands and the acquisition of new infections.

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