The purpose of this paper is to: (1) clearly describe how and when erythema infectiosum was first discovered; (2) explain how and when it became known as fifth disease and why this name is perhaps inappropriate; (3) describe the coincidental discovery of parvovirus B19; and (4) explain how the connection between parvovirus B19 and erythema infectiosum was finally made.

The discovery of erythema infectiosum

Erythema infectiosum was first described in 1889 by Tschamer, who thought it represented a milder form of rubella (German measles). Additional cases were described by Gumplowicz in 1891 and by Tobeitz in 1898. According to a review of cases presented by Shaw in 1905, the first person to suggest that this infection was a separate clinical entity was Escherich in 1896.

This condition didn’t actually become known as erythema infectiosum, however, until 1899, when it was given that name by Georg Sticker, a Professor of Medicine at Giessen University, Germany. Sticker’s description included the lack of perceptible fever at the time of presentation and emergence of red patches on the cheeks, consisting of large symmetrical blisters with red halos. The following day, the rash spread to the lower arms and thighs, as well as over the trunk, forehead, temples. This secondary rash consisted of round red spots or
larger, irregular, red patches (see Figure 1). Sticker noted that these eruptions tended to be slightly raised and that they were better felt than seen. These symptoms were most apparent on the third or fourth day of the infection and then rapidly resolved.

Sticker observed how erythema infectiosum spread through families and was consequently able to confirm its contagious nature. He also suggested that it belongs to the group of so-called “acute exanthems,” but that its particular course and skin symptoms excluded any confusion with scarlet fever, measles, or rubella (German measles). Sticker’s description of erythema infectiosum ends with an interesting acknowledgement: “In trying to find the specific cause we have been just as unsuccessful as other researchers have been with other kinds of kinds of infectious exanthems.” Indeed, the medical community would have to wait almost a century before the causative agent would finally be found.

Sticker’s description of erythema infectiosum had such an impact that for many years it was known simply as “Sticker’s disease.” Even as the term “fifth disease” became more common in some parts of the world, the reference to the Professor’s name persisted in Germany for years to come.

It began with the fourth

The origins of the name “fifth disease” go back to 1885, when a Russian physician named Nil Filatow was working on another childhood exanthem. His work was read at the Moscow Medical Society meeting on November 20, 1885, and later in published in German. As with Sticker, the list of childhood exanthems established up until this time included measles, scarlet fever, and rubella (German measles). Filatow argued for the existence of a fourth exanthem, which he called rubeola scarlatinosa. He reasoned that if patients could get this disease after having already had scarlet fever, or if contracting this disease did not protect them against getting scarlet fever in the future, then scarlet fever and rubeola scarlatinosa must be two different things. Filatow had seen evidence of this happening in one set of patients and appealed to doctors working in larger institutions to provide further evidence for the existence of this clinical entity.

One such doctor came along several years later named Clement Dukes. Dukes was a physician at a Rugby school in London, England, where he believed he had seen many patients similar to those described by Filatow. In 1894, he published an article in the Lancet in which he referred to rubeola scarlatinosa as epidemic roseola or rose rash. (This is not to be confused
with roseola infantilis, which was described in 1910 and later became known as sixth disease.11)

Dukes went into great detail describing what he believed were clear differences between scarlet fever, rose rash, and measles. He conceded that “In their elucidation they have entangled many of the ablest physicians, to our professional discredit and to the detriment of the welfare of our schools,” but insisted that “… They are as separable as typhus and typhoid fever.”

Dukes published a second article on this topic in 1900.12 In this paper, he noted that he “… would not venture to suggest an appropriate name for this disease,” and referred the question of nomenclature to the Royal College of Physicians of London. “Pending this authoritative decision,” Dukes “… tentatively employ[ed] the general expression of the ‘fourth disease.’” Ironically, this name not only became permanently associated with rubeola scælatinosa, but it also initiated a numbering system for the classic childhood exanthems that remains to this day.

The naming of fifth disease

Today, the fourth disease is regarded by most as a non-entity.13 In spite of the detailed reasoning presented by Filatow and Dukes, other studies could not establish that the fourth disease exists independently of scarlet fever, measles, or rubella, nor could a causative agent be determined. The most obvious flaw in the Filatow-Dukes logic is the fact that it is possible to get scarlet fever more than once.14 Thus, the idea that an infection confers immunity, and that any future infection that looks like scarlet fever must be something else, is incorrect.

Still, the idea of the fourth disease lasted long enough for the naming of fifth disease several years later. In 1905, a French physician named Cheinisse described erythema infectiosum in a weekly periodical called La Semaine Medical. He made reference to the three classic diseases of childhood: scarlet fever, rubella, and measles, and mentioned the so-called fourth disease, rubeola scælatinosa, in his introduction. His subsequent description of erythema infectiosum was entitled “Une cinquième maladie éruptive: le mégélerythème épidémique” (i.e., a fifth eruptive disease: the infectious erythema). It is unclear when exactly this name was changed to simply fifth disease, but the basis of its numbering can be traced back to Dukes “general expression of the fourth disease” in 1900.

The fact that fourth disease is now considered a non-entity suggests that the name fifth disease is perhaps inappropriate. While it is true that it was discovered after fourth disease, this numbering system makes the false assumption that Filatow-Dukes’ disease actually exists.

The discovery of parvovirus B19

Early attempts to connect erythema infectiosum with its causative agent included the inoculation of supposedly infected human sera in monkey renal cells.15 In another attempt, researchers obtained blood samples, throat swabs, and stool or rectal swabs from 27 infected patients and looked for pathological changes in various tissue cultures.16 Neither of these studies were conclusive. Another researcher went so far as to suggest that the causative agent of erythema infectiosum wasn’t infectious at all, but that correlation with the use of a margarine emulsifier indicated that it was based on nutritional and personal factors.17

Given the clinical course of erythema infectiosum (see Figure 2), it is easy to see why it was so difficult to identify its causative agent, parvovirus B19. While it is true that the lifetime prevalence of this virus approaches 90%, the viremia occurs before the emergence of the characteristic, red rash, and then rapidly resolves. Furthermore, the symptoms during the prodromal period are mild and non-specific. Many other cases are asymptomatic throughout the entire infection. It should be no surprise then that the discovery of parvovirus in human blood occurred coincidentally.

The human parvovirus was discovered by someone who had no interest in erythema infectiosum whatsoever. While working in
London, United Kingdom, an Australian virologist named Yvonne Cossart came across a collection of parvovirus-like particles while screening blood samples for hepatitis B. The sample containing these particles happened to occupy position 19 on plate B, which eventually led to the name B19.

Paroviruses had long been known to infect cats, rats, mice, minks, dogs, pigs, rabbits, geese, and cattle. But up until Cossart’s discovery, there was no evidence for parvovirus infection in humans. As a result, researchers were initially reluctant to refer to B19 as a true parvovirus, opting for terms like human parvovirus-like agent (PVLA) and human serum parvovirus-like virus (SPLV) instead.

Cossart later discovered the presence of parvovirus in the serum of a patient diagnosed with acute hepatitis. This coincidence raised the possibility of parvovirus being the elusive non-A, non-B virus. This, of course, turned out to be not the case, with hepatitis C being discovered several years later.

The search for the causative agent of erythema infectiosum was so elusive that it actually ended up taking place the other way around. Following Cossart’s discovery in 1975, a microbiologist named Anderson was busy studying parvovirus B19 at King's College Medical School in London. In 1982, he noted that “Infection with PVLA [parvovirus B19] is an apparently common event, occurring most often in childhood. Studies… show that that peak of antibody acquisition occurs between the ages of 4 and 6 years, and by the age of 16 one-third of subjects have PVLA antibody…” He also noted that “… three of the four blood donors from Dr Cossart’s group of nine who were followed up became ill shortly after giving blood; two complained of fatigue which was in one individual accompanied by leucopenia, while the third developed a rash.”

As seen in Figure 2, these symptoms and sequelae are classic to erythema infectiosum.

Figure 2: Schematic representation of the clinical course and laboratory abnormalities in normal hosts with parvovirus B19 infection. Note the biphasic timing of symptoms, during the peak viremia and again after the viremia has cleared. Rash, arthritis, and other symptoms typically associated with parvovirus B19 occur during the second period.
In 1983, this same researcher, obviously aware of what a parvovirus B19 infection might entail, provided epidemiological evidence of a parvovirus being the cause of erythema infectiosum. This connection was aided by a coincidental outbreak in north London and the use of parvovirus-specific IgM radioimmunoassay to confirm true cases. Further evidence on this outbreak was provided in 1984.

The final confirmation of parvovirus B19 being the cause of erythema infectiosum occurred when seronegative volunteers were inoculated with parvovirus from an asymptomatic donor. One week after inoculation, symptoms included mild illness, malaise, and other non-specific complaints, as well as viremia, excretion of the virus from the respiratory tract, and decreased levels of hemoglobin, reticulocytes, lymphocytes, neutrophils, and platelets. 17 to 18 days later, a second-phase of the illness with rash and sore joints lasting three days occurred in three of the four infected volunteers. (Refer to Figure 2 for an overview.) This constellation of symptoms was consistent with erythema infectiosum and explained why parvovirus infection could cause aplastic crisis in patients with chronic hemolytic anemia (such as sickle cell disease).

Conclusion

The associations between erythema infectiosum, fifth disease, and parvovirus B19 evolved gradually over almost 100 years. The turning points in this history include: (1) the recognition of a “different form of Rubella” by Tschamer in 1889; (2) the naming of erythema infectiosum by Sticker 1899 (and the evidence for its independence from scarlet fever, measles, and rubella); (3) the influence of Dukes and his general expression of fourth disease in 1900; (4) the reference to a fifth disease by Cheinisse in 1905; (5) the discovery of parvovirus by Cossart in 1975; and (6) the evidence of parvovirus as the causative agent by Anderson from 1983 to 1985.

It is true that some of these details amount to little more than historical trivia. But it is the authors’ hope that this overview will give students a greater appreciation of erythema infectiosum, fifth disease, and its elusive causative agent, parvovirus B19.

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References


