The fourth disease, 1900–1881, RIP

Sir—We strongly disagree with Martin Weisse's (Jan 27, p 299) [1] repetition of Powell's proposal that the fourth disease was a toxin-producing staphylococcal infection. We were workers involved in the description of staphylococcal scalded skin syndrome[2] and the work generally thought to disprove the existence of fourth disease.[2]

The existence of the fourth disease was seemingly laid to rest a decade ago, and should have been buried 120 years ago: it never existed.[2] To Weisse's rhetorical question "Is it a separate exanthum [sic]?" we respond with an unequivocal no: fourth disease was not staphylococcal scalded skin syndrome (SSSS) or any staphylococcal syndrome. It was a collection of misdiagnoses of rubella and scarlet fever seen in school outbreaks.[3,4] These misdiagnoses arose because physicians did not fully appreciate the variable and overlapping spectra of childhood exanthems.

We encourage readers who question these carefully researched conclusions to look at reference 3 and its citations, and to consider the following: SSSS (excluding localised bullous impetigo) uncommonly occurs beyond infancy and early childhood because antibody to staphylococcal exfoliative toxin is highly prevalent by then; school outbreaks of SSSS do not occur; most children with SSSS have foci of staphylococcal infection, unlike those with fourth disease; patients with SSSS have more extensive skin loss and denuding than the typically mild flaking described for fourth disease; and deaths from SSSS in otherwise healthy children are almost unheard of, whereas the more than 10% fatality in the scarlet fever-like fourth disease cases was typical of scarlet fever at the time.[3]

Data linking fourth disease to misdiagnosed rubella and scarlet fever are extensive and include the construction, by use of original 1896/1900 line lists, of epidemic curves for fourth disease that were specific for the various predominant characteristics of the observed exanthems.[3] These curves show that most of the 1896 cases Weisse discusses occurred in four cleanly separated epidemic waves, exactly 2 weeks apart—a classic pattern for rubella but unheard of for SSSS. To support SSSS, Weisse emphasises clinical observations, such as one describing tender skin. The attaching of specific meanings to single historically observed symptoms such as skin tenderness or sensitivity is problematic.[3] Rarely noted in fourth disease, skin sensitivity can hardly be taken to be a distinguishing symptom of a pseudosyndrome subsuming at least two other misdiagnosed exanthems, especially since it was also described for scarlet fever.[5]

All remaining clinical issues raised by Weisse were dealt with in the 1991 publication.[3] SSSS is highly inconsistent with many of the key features of fourth disease, but scarlet fever and rubella are not. The weight of evidence is still overwhelming: fourth disease never existed. All cases are explained clinically and epidemiologically by misdiagnosed scarlet fever (described in 1641) or rubella (established in 1881).

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1 Weisse ME. The fourth disease, 1900-2000. *Lancet* 2001; **357:** 299–301.
2 Melish ME, Glasgow LA. Staphylococcal scalded skin syndrome: the expanded clinical syndrome. *J Pediatr* 1971; **78:** 958–67.
3 Morens DM, Katz AR. The "fourth disease" of childhood: reevaluation of a nonexistent disease. *Am J Epidemiol* 1991; **134:** 628–40.
4 Dukes C. On the confusion of two different diseases under the name of rubella (rose-rash). *Lancet* 1900; **2:** 89–94.
5 Frank J-P. Scarlatine. In: Frank J-P. Traité de médecine-pratique: nouvelle édition—tome premier, genre II. Paris: J-B Baillière, 1842: 250–61.

Author's reply

Sir—David Morens and colleagues state that fourth disease was not SSSS or any staphylococcal syndrome and detail the disorder's inconsistency with the bullous form of SSSS. I agree with several of the distinctions they make between these two syndromes.

The expanded spectrum of SSSS was described in two early reports[1,2] as having several forms, including Ritter's disease, generalised bullous disease in older children (of which the most severe cases were formerly called toxic epidermal necrolysis), bullous impetigo, and staphylococcal scarlet fever. I used the generic term SSSS, since the clinical spectrum of fourth disease spans more than one of these clinical forms. I maintain that there is compelling evidence that fourth disease is most consistent with staphylococcal toxin disease, especially staphylococcal scarlet fever. My panel 3 shows that there are important discrepancies between fourth disease, rubella, and scarlet fever, and many similarities between SSSS and fourth disease.

Morens and colleagues comment that school outbreaks of SSSS are not reported. That staphylococcal scarlet fever (SSF), with or without bullae, can arise in clusters is supported by reports of family outbreaks,[1,3] one of which had a periodicity of 3 weeks between infections,[1] similar to that of fourth disease. Morens and colleagues further state that most children with SSSS have focal infection and fourth disease patients do not. With SSF, the form of SSSS most similar to Dukes' descriptions, focal infection was noted in only one of the 22 cases documented in three reports.[1–3] As opposed to patients with generalised bullous disease, patients with SSF do not have extensive skin loss, but instead have peeling, as is reported with fourth disease. Finally, the toxins and immunology of SSF seem to be different than the generalised bullous form of SSSS,[4] and we can only guess at the seroprevalence of antibodies against the various staphylococcal toxins a century ago.

I agree that interested parties should assess their reference, but I suggest revisiting Dukes' original report in light of arguments I put forward in my report. Not everyone feels that the fourth disease was laid to rest 10 years ago. Students of history can consider the evidence and make up their own minds.

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1 Margileth AM. Scalded skin syndrome: diagnosis, differential diagnosis, and management of 42 children. *South Med J* 1975; **68:** 447–54.
2 Melish ME, Glasgow LA. Staphylococcal scalded skin syndrome: the expanded clinical syndrome. *J Pediatr* 1971; **78:** 958–67.
3 Ladhani S, Newsom T. Familial outbreak of staphylococcal scalded skin syndrome. *Pediatr Infect Dis J* 2000; **19:** 578–79.
4 Lina G, Gillet Y, Vandenesch F, Jones ME, Floret D, Etienne J. Toxin involvement in staphylococcal scalded skin syndrome. *Clin Infect Dis* 1997; **25:** 1369–73.

Context and health outcomes

Sir—Zelda di Blasi and colleagues (March 10, p 757)[1] report on their systematic review of studies in which workers have assessed the effects of doctor-patient interactions on the outcome of care. They show that physicians who adopt a warm, friendly, and reassuring manner are more effective at interacting with patients than those who keep consultations formal and do not offer reassurance.

Di Blasi and colleagues emphasise a triple meaning of the notion of context in medicine. First, because they did a systematic review, through which studies are placed in the context of other relevant research. Second, the investigators broaden the term non-specific effects to context effects, instead of just illuminating the black box of the