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Letter to the Editor

The true historical origin of convalescent plasma therapy

The use of convalescent plasma, a strategy of passive immunization that has been applied in the prevention and treatment of epidemic infections for more than 100 years [1], has been proposed and performed also during the recent COVID-19 pandemic [2]. Generally the convalescent plasma use during the Spanish influenza A (H1N1) pneumonia (pandemic of 1918–1920) has been reported as its first application [3–6]. In fact, several studies conducted during this pandemic suggested that the convalescent plasma could be effective in reducing mortality risk, as later confirmed by the meta-analysis carried out by Luke et al. in 2006 [7], involving overall 1,703 patients from 8 suitable reports.

Actually, serotherapy from convalescent patients has been long used also before the Spanish influenza pandemic. For instance, it was tried as a medical treatment of acute paralysis in the 1916 New York outbreak of poliomyelitis [8]. Again in 1916, Nicolle and Conseil applied serotherapy to contain a small measles epidemic in Tunis [9]. In 1915 Hess used the same therapeutic option to treat mumps and prevent its testicular complications [10]. Finally, the Italian Francesco Cenci is credited to be the first to use convalescent serum as a therapeutic tool, to protect children exposed to measles infection [11].

It was possible to get the original article by Cenci [12], published in 1907 in an Italian pediatric journal (Fig. 1). The author was a public health doctor working in a small town of Central Italy near Perugia (Campello sul Clitunno, about 1,800 inhabitants in the early twentieth century [13]). Starting from the observation that, once cured of measles, it is very unlikely that a patient will fall ill a second time, and thus presuming the existence of some serum protective factor, during an epidemic outbreak in 1901 Cenci practiced a bloodletting of 600 mL to a 20-year old man, three weeks after recovery from measles. After blood coagulation, he collected serum in three sterilized tubes, adding a solution of phenic acid as a protective agent. The convalescent serum was

then inoculated to four children aged between 4 and 8 years, who did not contract measles after this treatment, unlike their cohabitant siblings. It has to be noticed that, to ensure safety of the product, 60 h before administration to patients, a portion of serum was inoculated into the peritoneum of a rabbit and also into the arm of Cenci himself, without this causing general or local reactions.

In these cases, however, human convalescent serum was successfully used as a prophylactic agent. This prophylactic application lasted several decades, as measles had a high mortality (6–7 %) in some populations [14].

In December 1906, there was another outbreak of measles in the Campello sul Clitunno area, with about forty sick children. Cenci successfully repeated prophylaxis through the convalescent serum inoculation. Moreover, in a child with a severe form of measles with pneumonia serotherapy made infection milder and duration of the disease shorter. This case unequivocally represents a therapeutic and not only prophylactic use of the convalescent serum, probably for the first time. As a matter of facts, Cenci reported that a similar treatment had been made on two children in 1900, in the Pediatric Clinic of Rome directed by Luigi Concetti [15], that was the first to use serotherapy against diphtheria in Italy, after the seminal studies by Emil Behring and Shibasaburo Kitasato [16]. Evidently, this therapeutic innovation was soon put into practice in an Italian suburban area, suggesting already then a good public health system. In fact, it may seem singular that this pioneering investigation was fully performed outside academic or research centres, and moreover in a deeply rural area of Italy, but it is well known that intuition and experimentalism at that time were typical of the whole medical class, which still breathed the cultural ground of the nineteenth century, namely a truly innovative period in the history of medicine.



XXIX.

Dott. Cenci Francesco

Ufficiale sanitario in Campello sul Clitunno

**Alcune esperienze di sieroimmunizzazione
e sieroterapia nel morbillo**

È noto a tutti che il morbillo, sopportato una volta, abbastanza raramente si contrae una seconda. Mentre assai facile è il contagio di questa malattia esantematica, assai difficile è la reinfezione dell'organismo; e ciò per il fatto dell'immunità, che si acquista dopo la prima infezione.

Tra i tessuti che contengono in maggior quantità le sostanze anti-infettive è il sangue, e specialmente il suo siero, che talvolta ha un naturale potere battericida, come quello dei topi che immunizza gli animali dal carbonchio.

Oltre però a questa *immunità naturale*, ve ne è un'altra *acquisita*, che ha per causa una pregressa spontanea infezione più o meno grave, dalla quale si è guariti per resistenza organica. Tale immunità, che è fatto noto per molte infezioni (scarlattina, morbillo, sifilide, tifo, difterite, ecc.), e che può durare per tutta la vita, od un tempo più o meno lungo, fu spiegata diversamente dai vari batteriologi di questi ultimi tempi, ma ora è ritenuta dipendente dalla produzione di antitossine o di sostanze antibatteriche o anticorpi, che impedirebbero l'azione delle sostanze velenose prodotte dai batteri o lo sviluppo stesso di essi. La teoria delle catene laterali di Ehrlich è quella che domina ora il campo della scienza nella produzione delle antitossine e degli anticorpi in genere. Per essa i microrganismi od i loro prodotti morbosi si unirebbero ad una parte delle cellule dell'organismo, cioè agli amboettori specifici in modo da neutralizzarle. Le cellule eliminerebbero queste molecole organiche saturate e reagirebbero col produrre amboettori specifici nuovi, ed in eccesso, in modo che poi se ne distaccherebbero ed andrebbero in circolo. Il sangue così conterrebbe nel suo siero sostanze immunizzanti spe-

Fig. 1. First page of the paper by Francesco Cenci, 1907 [12].

CRedit authorship contribution statement

Piero Marson: Writing - original draft, Conceptualization. **Andrea Cozza:** Investigation. **Giustina De Silvestro:** Supervision.

Declaration of Competing Interest

We declare no relevant conflicts of interest.

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