

Giuseppe Brotzu and the Discovery of Cephalosporins.

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Giuseppe Brotzu (1895-1976) was for over thirty years Professor of Hygiene in the Medical Faculty and Rector (1936-1945) of the University of Cagliari. As Superintendent of the Public Health of the Sardinian Regional Government he campaigned to eradicate malaria from Sardinia with the financial support of the Rockefeller Foundation.

As a scientist, his fame is due to the discovery of cephalosporins that he made in Cagliari at the end of the "2nd World War". The hypothesis that led Brotzu to the discovery of the cephalosporins originated just in the context of surveys on the spread of the typhoid fevers in Cagliari.

In spite of the fact that many young people were used to swimming in the polluted waters of "Su Siccu" (Fig. 1), a place where Cagliari sewage waters were discharged, and to eat raw shellfish, they did not usually become ill.

At that time the epidemics of typhus were very frequent in many Italian cities with similar bad hygienic conditions. In order to explain this phenomenon Brotzu hypothesized the presence of a microorganism able to inhibit the growth of *Salmonella typhi* and the spread of the infection; in fact he was not only an excellent microbiologist but was also aware of the discoveries of Fleming, Chain and Florey on the effects of penicillin. The researcher was also aware of the necessity to demonstrate experimentally his assumption.

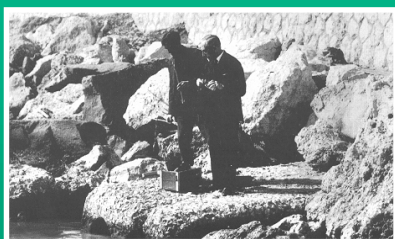


Fig. 1 - At "Su Siccu" to take samples for analysis.

Although technological means were quite deficient, he managed to isolate an antimicrobial agent (*Cephalosporium acremonium*) from the sewage fluids and demonstrated, in agar cultures, the inhibitory effect on Gram-negative bacteria, as *Salmonella typhi*, *Vibrio Cholerae*, *Brucella melitensis*, etc. (Fig. 2). This was very important because, in those years, there was no pharmacological agent acting on Gram negative bacteria.

Brotzu extracted the antibiotic principle from liquid cultures and purified and concentrated it in small volumes. He produced the so-called "micetina", an extract containing the *Cephalosporium* but also many impurities.

Now it was necessary to demonstrate the effectiveness of the substance in the therapy of infectious diseases in humans: a preparation effective in *in vitro* experiments is not always useful for the treatment of human pathologies.

He injected the extract both locally and by systemic therapy: it showed its effectiveness in the treatment of infected surgical wounds and also in some systemic pathologies such as typhoid fever and brucellosis. No noticeable side effects were recorded.

Even if he was aware of the importance of his discovery, owing to the lack of facilities and financial support, he was unable to study further the activity of the fungus and to purify the substance for a safe use in medicine.

Thanks to Blyth Brooke, a medical officer of the allied troops in Sardinia, Brotzu sent a sample of "micetina" and a copy of his work with the description of *C. acremonium* to Florey, at the Oxford School of Pathology. At that time this center was probably the most important for the studies on antibiotics, both for the great scientific personalities (Florey, Abraham) here operating as well as for the availability of modern technologies. The English laboratory could take advantage of the unique experience gained in the study of penicillin. Abraham identified three antibiotic substances in the "micetina": cephalosporin P, cephalosporin N (latter named penicillin N) and cephalosporin C. But only cephalosporin C attracted the English researchers because of its characteristics: resistance to penicillase, wide range of action and chemical adaptability. So the happy intuition of Brotzu became one of the most important tools in the therapy of infectious diseases.

For his discoveries in 1971 Brotzu was awarded the honorary degree in Science by Oxford University.

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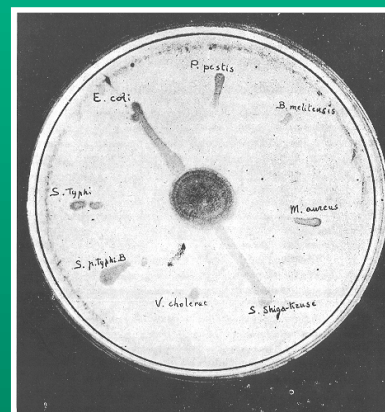


Fig. 2 - Three Day colonies. The undeveloped area indicates the potency of the antibiotic on each species.