

All ptomaines fault! The strange story of the *cadaveric alkaloids*, from forensic medicine to molecular biology passing through the asylum

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Abstract. This essay attempts to reconstruct the story of ptomaines, discovered in 1872 by the Italian chemist Francesco Selmi. This work provides a brief summary of this story, focusing also on an emblematic clinical study by the end of the 19th century, written by Raffaele Canger, a doctor who worked in the Asylum of Nocera Inferiore in Italy. The main thesis of Canger's paper is that the transient neuropsychiatric symptoms, which can occur during influenza or other infectious diseases, are due to a toxic delirium caused by the direct action of ptomaines on the brain with subsequent *restitutio ad integrum*. The importance of the discovery of ptomaines was discredited for a very long time, but recently, with the contribute of molecular biology it was established again the role of these molecules in human pathology.

Key words: ptomaines, Francesco Selmi, biogenic amines, asylum, Raffaele Canger, molecular biology, toxins

Introduction

The amino acids, under the action of the decarboxylases, form CO₂ and the corresponding amine. This process takes place in animal tissues and in microorganisms too. Among the amines that are formed, there are putrescine and cadaverine which originate respectively from ornithine and lysine. Putrescine is a precursor of the two main polyamines: spermine and spermidine which have long been identified as molecules capable of controlling the synthesis of nucleic acids in rapidly growing tissues (1).

In 1872 the Italian chemist F. Selmi discovered *cadaveric alkaloids*, such as cadaverine and putrescine, which derive from the decomposition of tissues and he called them *ptomaines*, from the Greek term *πτῶμα* (corpse). This discovery immediately proved to be of medico-legal interest, as it made it possible to avoid interpretative errors in case of the suspicion of poisoning by the introduction of vegetable alkaloids (2).

During 150 years of medical history, *ptomaines* have been the subject of debate, credit and discredit, in relation to their role in diseases. The aim of our work is to provide a brief summary of this story, focusing on an emblematic clinical study by the end of the 19th century, authored by Raffaele Canger, doctor from the Asylum of Nocera Inferiore in Italy (This asylum hospitalised patients from five districts of southern Italy: Cosenza, Foggia, Bari Salerno and Campobasso. It was founded in 1882 and permanently closed in 1998).

Materials and methods

In order to understand the consideration that the recent discovery of cadaveric alkaloids had at the end of the nineteenth century in clinical practice, concerning nervous and mental pathologies, we have examined an article taken from the magazine of the Asylum of Nocera Inferiore (Italy) concerning the pathology neuropsychiatric related to influenza infection (3).

This work is framed in the development of knowledge on the so-called ptomaines discovered by F. Selmi. A search on PubMed revealed the presence of ten articles dated from 1884 to 1919 for the keyword *ptomaines* and twelve articles for the keyword *ptomaine* from 1886 to 1932.

The research work has been integrated up today, by inserting the keywords putrescine and cadaverine, which are largely contained in the class of *ptomaines* according to their discoverer.

Discussion

The main thesis of Canger's paper is that the transient neuropsychiatric symptoms, that can occur during influenza or other infectious diseases, are due to a toxic delirium caused by the direct action of ptomaine on the brain, with subsequent *restitutio ad integrum*.

In fact, this scholar states:

"We have already pointed out that there is a certain analogy between the delirium of infectious diseases, and the one that follow the most varied accidental poisonings, especially for alkaloids (hyoscyamine, atropine, quinine, morphine, cicutin, etc.), whose pathogenesis is to be sought in the deleterious action of these substances on the nerve cell. Now, in order to microorganisms to be able to explain analogous effects, it must be admitted that they disturb the vitality of the tissues either by their presence, or by their secretions, or by the constituent substances of their body.

The most generally accepted hypothesis, because it is confirmed by the experiment, is that among the products of the bacteria's material exchange there are substances belonging to the organic bases: which, given the general reactions of alkaloids, Selmi named ptomaines" (In the original text: "Abbiamo già fatto notare come esiste una certa analogia fra il delirio dei morbi infettivi, e quello in seguito ai più svariati avvelenamenti accidentali, specie per alcaloidi (iosciamina, atropina, chinino, morfina, cicutina ecc.), del quale la patogenesi è da ricercarsi nell'azione deleteria delle dette sostanze sulla cellula nervosa. Ora perché i microorganismi riescano a spiegare analoghi effetti, è da ammettersi che essi turbano la vitalità dei tessuti o per la loro presenza,

o per le loro secrezioni, o per le sostanze costituenti il loro corpo. La ipotesi più generalmente accettata, perché confermata dallo sperimento, è che esistano tra i prodotti del ricambio materiale dei batteri sostanze, appartenenti alle basi organiche: alle quali, aventi le reazioni generali degli alcaloidi, il Selmi ha dato il nome di ptomaine").

In this historical period, studies on bacterial toxins were showing that the direct action of bacteria in infected tissues (4) was not the only way to cause diseases, which means that authors are often hesitant to distinguish between toxins and ptomaines.

However, experimental data were often provided to support the importance of ptomaines in the pathogenesis of diseases (5). So, some authors can claim that "It is interesting to observe the manner in which the humoral pathology of former times is reappearing in the nowadays pathology under the name of Ptomaines" (6).

Very soon the fame of the ptomaines would have declined, limiting themselves to the field of food poisoning and continuing to compete for spaces with pathological pictures, such as botulism. Also, in these cases neurological symptoms were attributed to the presence of ptomaines (7).

Finally, in our time the diagnosis of ptomaines poisoning has become a "discarded diagnosis" (8). But is this really the case? It would seem not.

The amines that are produced by the decarboxylation of amino acids are called biogenic amines (BAs), which, in addition to those mentioned previously in this paper, also include monoamines such as histamine, serotonin, tryptamine, etc. It is currently recognized that the ingestion of biogenic amines with food, including those previously defined as ptomaines, is the cause of symptoms characterized by gastrointestinal disorders, headache and hypertension. This phenomenon happens when the level of ingestion exceeds the organism ability of clearance linked to intestinal amino oxidases. Cadaverine and putrescine alone have low toxicity, however they can amplify the effects of histidine and tyramine by inhibiting the enzymes that metabolize them (9, 10).

The symptoms, detected by Canger in his patients, differ from those of a purely neurological nature which he calls hallucinatory delirium:

“Therefore, assuming as a pathogenetic foundation of the psychosensory disorders of influenza, as well of other infectious diseases, the direct action of ptomaines or toxins on the brain, we will rightly call the sum of these phenomena toxic delirium” (In the original text: “Ammesso, adunque come fondamento patogenetico dei disturbi psicosensoriali dell’influenza, come di altri morbi infettivi, l’azione diretta delle ptomaine o tossine sul cervello, noi a buon diritto chiameremo delirio tossico l’assieme di questi fenomeni”).

Interesting insight, since, as is currently known, BAs can act as pseudo-neurotransmitters in the brain. Furthermore, regarding their role in bacterial infections, polyamines seem to assume importance again in researchers’ studies. Cadaverine, putrescine and spermidine are the most common bacterial polyamines and they can regulate the expression of certain virulence factors during infection (11).

Putrescine, spermine and spermidine regulate translation and transcription at the cellular level, immune response, cell proliferation and differentiation, apoptosis, ion channels and cytoskeletal signaling and other key phenomena, from a cellular biology point of view.

The multiple functions of polyamines and their role in pathology and in maintaining the health of the organism are currently being clarified. Both their excess and their deficiency can be the basis of morbid conditions (12).

Interestingly, given the new molecular biology data, the large number of corpses produced during the COVID-19 pandemic has recently raised the problem of the possible contamination of cemetery by soil BAs, such as cadaverine and putrescine with carcinogenic potential (13).

Conclusions

The discovery of the ptomaines, presented by Selmi on the 25th of January 1872 at the Academy of Sciences of Bologna, was the result of the great acumen and skill of a scholar who worked in a period and in an environment in which the development of applied sciences was difficult and scarcely supported (14). However, the discovery had rapid resonance and was also held in

high regard in medical practice, as demonstrated by the Canger’s paper. It is not surprising that the doctor from the asylum of Nocera Inferiore always referred to bacteria when talking about the influenza that had affected his patients. It was a time when Koch’s bacteriology and postulates dominated medical science. Nor could the discovery of filterable agents make the big picture clear. Virus was a term applicable to any toxic or poisonous factor capable of causing disease and, according to Pasteur’s view, each virus was a microbe (15).

This microhistorical study that focus on the paper of Dr. Canger, in relation to the research of F. Selmi, teaches us that every scientific discovery is a process which inevitably have to be carried out in the long term and its value is often measured in relation to other supervening discoveries and the cultural background in which they are generated and received.

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