The question of mycotic splenomegaly

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The lesions first described in 1905 by GANDY and, afterwards, studied in detail by others, among which D. SYMMERS, A. O. GETTLER and W. M. JOHNSTON in 1919 and CARLO GAMA in 1924, were lately the subject of researches by several investigators who attempted to demonstrate their parasitic nature.

In 1926, NANTA, PINOV and GRUNY presented to the Society of Biology, in Paris, a note on several cases of splenomegaly operated on at Algiers by CONSTANTINI, in which the spleen showed a granulatemonous transformation and sclerotic and siderotic adhering hard nodules, disseminated, of a ferruginous color, measuring 1 to 2 mm. in diameter and containing giant cells of the type of those of foreign body. What, however, called most the attention was the presence of long bands, 5 to 15 micra in diameter, rectilinear or wavy, sometimes refringent and not staining, or, sometimes, stained as if they were conjunctive bundles in basophile degeneration. In these lesions the authors found germs which they could not cultivate and which were a spirochete with a few loose spirals and a streptobacillus, only observed in the nodules and forming cysts comparable to those of the myxobacteria.

That initial communication was followed by the notes presented afterwards to the Academy of Sciences of Paris, respectively by NANTA and PINOV, on a myxobacterian splenomegaly and on a synbacterium isolated from cases of splenomegaly. Already there were being put apart the spirochaetes as non constant and Synbacterium splenomegaliae is described as forming cysts sometimes with the loss of collagen fibres, which can also form bands adorned with clavae and spines analogous to those found by MAGROU in the grains of experimental staphylococcic botryomycosis. The germ which is now described as a coccus or as an encapsulated diplococcus, kills the rabbit and the Guinea pig in less than 24 hours, producing congestion of the spleen and adrenals. In the Guinea pig, subcutaneously, a gelatinous oedema in which are found the encapsulated germs and, sometimes, long filamentous forms, is obtained at the place of the inoculation.

The blood of the inoculated animals does not coagulate and shows a decrease in the number of leucocytes. These, may appear changed and containing frequently cocci and diplobacilli. The part that this synbacterium plays in the production of the cases of splenomegaly in which it has been observed is not then considered as proved, but PINOV presumes that it should produce an acute febrile disease, whose chronic state would correspond to the studied conditions of splenomegaly.

In the beginning of 1927, PINOV and NANTA's ideas already had evolved and in a note presented again to the Academy of Sciences of Paris, these authors for the first time attributed to the pathogenic action of fungus of the Aspergillus nidulans group the cases of splenomegaly so far
studied by them. The pseudo-cysts at first attributed to the sybacterium would
represent now fructifying organs, now ornamental organs of the peritheca:
*Gama's nodules, they say, are mycotic nodules and the cases of splenome-
galy with Gama's nodules are cases of mycotoma of the spleen. The bacte-
ria which were found probably are only brought in, introduced by the
fungus, as secondary infection. In the same note PINOY and NANTA sug-
gest the possibility of the Egyptian splenomegalv having the same mycotic
etiologie and they insist upon the prevalence in Algeria of such mycosis
of the spleen. In a note presented to the Congrèse pour l'avancement des
Sciences, in CONSTANTINE, in the beginning of 1927, PINOY proposes
for the fungus isolated from the spleen which he had studied the creation
of a new species which he calls *Aspergillus nantae* and which would be
distinguished from *Aspergillus nidulans*, among other characters, by the
absence of perithecia in the cultures.

Not long after P. ÉMILE-WEIL, GRÉGOIRE and FLANDRIN presented
to the Medical Society of the Hospitals of Paris seven Parisian
cases of primitive mycotic splenomegalv out of sixteen spleens obtained
surgically or on autopsy. The authors insist upon the difficulties of the
clinical diagnosis and point out the interpretation of the splenic lesions as
due to the infection by a fungus. They describe GAMA's nodules as sur-
rrounded by giant cells which englobate spores, mycelial fragments and
granulations of a pigment which stains in blue with the potassium ferro-
cyanid. The nodules would be full of mycelial threads which, however,
would show none or little staining by the blues. *Aspergillus*-like heads are
also found by P. É.-WEIL, GRÉGOIRE and FLANDRIN who still point
out the extensive invasion by the mycelium of the arterial and venous
walls. Also large spores, encapsulated, with one or more coverings were
pointed out in these Parisian cases just as they had been in the Algerian
ones by NANTA and PINOY. P. É.-WEIL, GRÉGOIRE and FLANDRIN
consider that the appearance of the fungus is so characteristic and con-
tant that its existence could not be questioned even if the cultural exper-
iments should fail. In two cases, the three quoted authors succeeded in
isolating from the spleens under examination a fungus different from that
of NANTA and PINOY, from which they concluded that the mycotic splen-
omegalv can be produced by different species of aspergilli.

In Paris P. ÉMILE-WEIL, GRÉGOIRE and FLANDRIN, therefore,
and soon after ASKANAZY and SCHWEIZER, confirm and amplify the
conclusions of NANTA and PINOY. The latter authors, in their turn, find
support to their ideas in one experiment which according to them shows
the virulence of the fungus culture which, venously, is able to kill a rabbit
in 8 days causing lesions comparable to those produced by *Aspergillus fu-
migatus* and comparable, to a certain extent, although much more acute,
those observed in cases of human splenomegalv.

Other cases of SABRAZÉS and MURATET, BÉCART, COYON,
WILLEMIN CLOY and BRUN, ARSEN PRODANOS have been published
and presented in support of the same ideas of the mycotic nature of cer-
tain cases of splenomegalv.

The wide authority of some of the investigators who brought all
such contributions, particularly the recognized experience of PINOY who
is one of the most able men among those engaged in work on medical
mycology, appeared to envalue the observations with such guaranties of exactness that the existence of mycosis of the spleen and of its intervention in the production of splenomegaly of the type observed in BANTI's and other diseases turned to be considered certain.

It did not take too long, however, until restrictions began to be made concerning the relation which might exist between the mycotic infection and the observed morbid signs. OBERLING in the beginning of the present year, found siderotic nodules in a case of lymphatic leucaemia and considered them constant in the cases of BANTI's disease, the typical nodules, the mycotic nature of which he does not question, having been demonstrated abundantly even in material from one of the cases studied by BANTI himself and kept at the Pathological Institute of Strasbourg. The presence of lesions considered as mycotic in a great number of cases of various affections led OBERLING to doubt that they might be due to the primitive infection and to admit that these lesions represented secondary implantation of fungi in pre-existing lesions of variable nature.

A. GOSSET, S. BERTRAND and J. MAGROU, after inoculating a suspension of *Aspergillus nantae* spores in the splenic pulp and in the perirenal tissue of a rabbit, obtain at the end of 43 days a splenomegaly accompanied with ascitis and pseudo-pulmonar tuberculosis. The search for mycelial filaments in the sections of the inoculated animal was negative, only elements of doubtful nature being found, perhaps degenerated fragments of the inoculated fungus. The authors think on the possibility of a filtering form of *Aspergillus*. To suppose that the splenomegaly and the other observed lesions did not represent a consequence of infection by the fungus but delayed results of the traumatism or of the introduction of foreign bodies or substances into the mass of the splenic parenchyma is more logical and natural.

The first clearly discordant voice out of the unanimous conformations of NANTA and of PINOY's works, came from CARLO GAMNA, one of the observers who first studied the siderotic nodular lesions of the spleen. GAMNA refers that he observed the nodules described by him in cases of BANTI's disease, splenomegalic atrophic cirrhosis, constitutional haemolytic jaundice, of STILL's disease, whilst OBERLING had found them still in cases of pigmentary cirrhosis LAENNEC's atrophic cirrhosis, calculous cirrhosis, etc. Besides, CHRISTELLER and PUSKEPELIES, EPPINGER, KLINGE and HENNINGS, SMEGMUND, WOHLLWILL, SCHUPPISER, KRAUS, KLINGE, NICOD, DAY and JERGUSSON had verified identical lesions in various forms of chronic splenomegaly, without seing in them any sign of mycelial formations.

GAMNA reminds that the filamentous and siderotic formations of the pseudo-mycelium found in the nodules of the spleen are known of the histologists as a result of regressive transformations of elements of the tissues and that their only presence is not reason enough to admit the possibility of a case without precedent in the history of medical mycology, of primitive and circumscribed infection by a fungus of an organ such as the spleen.

Just after GAMNA, LANGERON makes a detailed study of PINOY and his coworker's observations and conclusions. He shows that the cultures from which the fungus accused of producing the mycosis of the spleen
was isolated were impure cultures, that the fungus is incriminated after having been so a spirochaete and a mycobacterium, that the identification of the Aspergillus since the beginning was hesitating, that the designation of mycetoma is incorrectly applied to the supposed mycosis of the spleen where the presence of pus and fistulae is not pointed out.

The notion of splenic mycosis, such as PINOY, NANTA and their coworkers had attempted to establish it, was thus already deeply shaken when we decided to make a revision of the material from splenomegaly cases existing at the Department of Pathology of the Instituto Oswaldo Cruz of Rio de Janeiro (1). We verified then the existence of many cases in which there had been pointed out siderotic nodular lesions of a type entirely identical to that described by GANDY, SYMMERS, GAMNA and many other authors. Some of these Brazilian cases had already supplied material for an inaugural dissertation issued from the Laboratories of the Instituto and presented to the Faculdade de Medicina of Rio de Janeiro in 1923 by Dr. HERMINIA DE SOUZA ASSIS. Of these cases, some did not show lesions that might lead to confusion with mycotic lesions. Others there were, however, in which the individualization of GANDY-SYMMERS-GAMNA's nodules was very prominent, its aspect resembling really that of mycetoma grains and, furthermore, that of the grains found in staphylococcic botryomycosis.

In the sections stained by hematoxyline and eosine, are found, sometimes in a great number, scattered in the tissue of the organ, more frequently near the vessels, masses of homogeneous appearance (Fig. 3) and different shape. They may be roundish, in form of band or of clue, and are stained in rose at the periphery, colourless or grayish at the center, usually accompanied by filamentous forms of the same colour isolated or forming more or less compact bundles, whose elements are different from one another. Often these filaments roll themselves up around a vessel. Beside such formations stained in rose or in clear-gray and, although anhists, comparable sometimes to mycetoma grains, are found in other points of the section filamentous elements (Fig. 4), yellow greenish or more or less intensely blueish, rectilinear, sinous or clue-like, sometimes bifurcate, of irregular diameter, formed of roughly quadrangular segments separated by clear linear spaces, free from any covering and formed of a compact and anhist substance. In some points, roundish formations (Fig. 5) constituted by a central clear space surrounded by several layers of filamentous elements stained blue, dark-gray or greenish-yellow, arranged into concentric circles or into parallel undulations, appear to correspond to transverse sections of deeply changed vessels.

The aspect of all of these structures may at first sight impress one as resembling that of mycelial elements and of mycetoma grains. A minute observation, however, of the spleen sections from the Brazilian cases of splenomegaly which we have had the opportunity of examining, permitted us not to verify the presence of a single element which unquestionably might be attributed to fungi. Much on the other hand, all the for-

(1) Acknowledgements to our colleagues of that Department, Drs. MAGARINOS TORRES and OSWINO PENNA, who put at our disposal their collections.
mations found showed transitions to such other elements with which visibly could not be considered mycelial and in fact were connected with changes of tissues with which are observed in much different morbid conditions. It is as such that, in accordance with GAMNA and with LANGERON, we interpret the structures observed in the siderotic nodules of the spleen in the Brazilian cases.

Now we should refer here the very great difficulty that one finds sometimes when the correct identification of elements of fungi in the tissues is sought. It has not been long since a patient, a student of medicine, came to the Dermatological Clinic of the Medical School of Rio de Janeiro. He presented two great ulcerous-crustous lesions of the fore-arm which clinically we considered as suspicious of mycotic origin. Having been performed the biopsy, the sections showed many filaments sometimes branched and gemmating which seemed to confirm the clinical suspicion. None of the filamentous formations in question showed, however, the indubitable aspect of mycelium and, as the cultural tests yielded no concluding results and as we only isolated common fungi from such open lesions, the hypothesis of mycosis was gradually discarded. On making a better inquiry we were able to learn from the patient that he was an epileptic and that he had been since long under treatment with BARASCH'S specific which, as it is known, has as its base the bromide of potassium. We were dealing with a case of intoxication by this salt, thus a case of bromide, which was followed by complete cure upon the pure and simple suppression of the intoxicating medicine.

This case was very instructive to us and made us acquire and experience which has been very useful in our searches for fungi on sections of animal tissues.

We think that in the case of splenomegaly in which siderotic nodules are observed, all those aspects which PINOY, NANTA and others have been describing lately as belonging to a pathogenic Aspergillus are degenerative.

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