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Lipochagomata Genii or Lipochagomata of the Cheeks, Characteristic Lesions of Acute Trypanosomiasis Cruzi in Children under Three Years of Age.

By MIGUEL E. JÖRG and RAMÓN S. FREIRE

Antecedents of the description of lipochagomata.

MAZZA and FREIRE (11) studied in 1940 four cases of acute trypanosomiasis cruzi in children of 2½, 3½, 9 and 15 months of age. They described, among other symptoms and signs characteristic of this illness, a facial semeiologic element that appeared at the 15th, 5th, 28th and 10th day of the evolution of the disease. This sign was described as follows: "nodular formation in the thickness of the cheek, inflammatory in nature, a hard cellular infiltration, bilateral, located in the place that corresponds anatomically to Bichat's fat pad". At the same time (as described in the above mentioned publication) these authors found and described as subcutaneous lesion of acute trypanosomiasis, nodular masses found within the hypodermis of different parts of the body, calling them Chagomata (from Chagas, discoverer of the illness, and "oma", suffix classically meaning tumoral volume). Microscopically they found an hypodermic cellulitis accompanied by an intense inflammatory cytosteatonecrosis within which large amounts of leishmania bodies of *Trypanosoma cruzi* could be found. This circumstance led those authors to call this infiltration of the cheeks "*lipochagomata genii*", using the prefix lipo as a reference to its localization in Bichat's fat pad. Its pathology resembled that of the subcutaneous chagomas, although at that moment and until the date of this publication, due to the logical difficulties in the realization of external facial biopsies, there had been no proof of such lesions. This situation has been satisfactorily resolved by the second of the authors of this publication (FREIRE).

Therefore, the purpose of this publication is to expose the first studies on the pathology of lipochagomata genii.

It should be mentioned that the first observations of lipochagomata, although not stressing its particular localization and pathology, were due to Salvador MAZZA's sagacity, to his acute sense of observation and his fidelity in noting the symptomatology of all the patients he observed. In 1934, on a trip to the province San-

tiago del Estero, MAZZA showed JÖRG, who accompanied him, a 3 month old nursling who was febrile, had hepatic and splenic enlargement and suffered from such formations that are even apparent in the photograph taken (2, p. 17, Fig. 5). This fact was not noted as no trypanosomes were found in a thick film from the child's blood nor could a bigger quantity of blood be extracted for inoculation tests in experimental animals. At that time, during a joint observation, MAZZA's attention was drawn to the same fact in another patient, Ceferina Pantoja, of Jujuy (1, p. 10), but he interpreted it as part of the edema and facial infiltration that was present in the little girl. MAZZA had to face continuous attacks and obstinate, sometimes malevolent opposition when he began to prove that trypanosomiasis cruzi or Chagas' disease was as a national epidemic a problem of the first order, owing to the abundance of cases and the serious nature of the lesions. This made him very cautious when expressing new concepts or interpretations.

That is why these lesions were noted as a simple part of the general symptoms of the illness, without attaching to it the importance they deserved. So much so that in 1936 MAZZA, ROMANA & ZAMBRA (5), in their description of the clinical characteristics of an acute case refer to a "pasteboard-like infiltration . . . in the midst of the cheek . . . well defined . . . painful to pressure", but without attaching much importance to it. It turned out to be in this case a deep reaction, in contiguity to a dermoepidermic lesion as a result of the primary infection, and corresponds to what was later called "contiguous lipochagoma or lipochagoma by contiguity". In the same manner, in 1937, MAZZA & BENITEZ (6), whilst enumerating the symptoms of an infant (Ramon Sotelo, Case No. 5) with trypanosomiasis cruzi, mention the presence of "on the left cheek, apparent to inspection and palpation, a nodule of hard infiltration of the size of a pidgeon's egg, with superficial venous network system, very painful to the touch, which has been marked in white in the photograph of Fig. 24". In the figure quoted above, the gross tumescence of the process can be appreciated. The patient presented dacryoadenitis, orbital cellulitis (tenonitis), with severe exophthalmos, palpebral paralysis, lagophthalmos and conjunctival ecchymosis on the same side as the cheek nodule. Therefore it was presumed that this nodular formation had developed by spread being contiguous to the primary infection of the orbit.

But, also in 1937 in Tucuman, MAZZA, COSSIO & ZUCCARDI (7) while describing the first acute and grave case of trypanosomiasis cruzi mention the presence of two elements: a) lipochagoma genii in contiguity with an inoculation chagoma described as follows: "in

the right cheek the skin is distended, pasteboard-like, hard, warm and red, and observable under it, a hard nodule of the size of a nut; using a combined palpation of the healthy buccal mucosa and the skin, we conclude that this nodule is isolated". b) a lesion which was later called hematogenous lipochagoma genii described as follows: "a similar nodule (to that described above, note of the authors) is verified in the thickness of the left cheek, where the edema is hardly perceptible".

By the characteristics of independent development of the contiguity of inoculation, the nodule which was observed and described in the left cheek of this case is, without any doubt, the first mention of what was later to be called "hematogenous lipochagoma genii", that is to say, inflammatory infiltration of Bichat's fat pad by sanguineous parasitic spread, and not contiguous to the primary infection.

But it was really in 1938 on a trip to Villa Angela, that MAZZA, based on clinical material accumulated by FREIRE and pathological experimental evidence supplied by JÖRG, noticed that the lipochagomata were manifestations of unique importance in the symptomatology of trypanosomiasis cruzi and therefore decided to study them with careful attention.

The possibility of apparition of inflammatory tumours or hypodermic infiltrative plates as secondary manifestations of parasitic localization because of blood spread was effectively described by MAZZA & JÖRG (4) while studying the natural mortal infection of trypanosomiasis cruzi in a local race of chihuahua dogs from Jujuy (called there "pila" dogs). Its pathological study in the post-mortem examination revealed lesions in the subcutaneous tissue defined as a disseminated multifocal hypodermatitis associated to an incipient cytosteatonecrosis and subsequent lipophagic granuloma.

MAZZA & FREIRE (8) in 1939 already make definite reference to that infiltrative sign caused by *Trypanosoma cruzi* while describing the clinical history of the nursling Agustin Vazquez (Case 13 p.39). In the photograph that illustrates that publication, both infiltrated cheeks are evident.

In 1940, MAZZA & FREIRE (11) described the chagomata, both from a clinical and pathological point of view, as being a characteristic manifestation of the localization of *Trypanosoma cruzi*, together with its subsequent inflammatory process of the subcutaneous tissue, specially the panniculous adiposus. In close relation to this study, MAZZA & FREIRE (12) also described the lipochagomata genii in extenso and with that designation, classifying them as isolated symptomatologic entities in trypanosomiasis



Plate I. Three cases of acute trypanosomiasis cruzi showing lipochagomata genii.

Fig. 1. Case 1 with multiple subcutaneous hematogenous chagomata (arrows). Digital palpation of the lipochagomata of cheek and arm.

Fig. 2. Case 2 with hepatosplenomegaly (marked with ink).

Fig. 3. Case 4 with multiple subcutaneous chagomata (marked with ink).

cruzi, stressing textually their importance in the title of the publication "Diagnostic importance in infants with acute forms of Chagas' disease without other apparent manifestations".

The significance of the verifications of MAZZA & FREIRE, and in this resides the importance of the knowledge of lipochagomata, is that although they frequently appear as part of a group of proper symptoms of trypanosomiasis cruzi (ophthalmolymphadenitic complex, subcutaneous chagomata, schizotrypanids, lymph-

adenopathy, enlargement of liver and spleen, fever, etc.), they also appear in numerous cases in which they are the sole objective symptom that leads us immediately to the diagnosis of Chagas' disease, specially in children with undefined processes, of common non-specific symptomatology, usually bound to the frequent summer ailments of the children in the interior of the country (fever, lack of appetite, bronchial catarrh, vomiting, restlessness, inconsolable crying, obstinate cough and even lethargy, etc.).

Up to the present, we have not come across cases that could deny the nosological postulation that acute febrile state plus cheek infiltrations with the characteristics of lipochagomata *genii* is equivalent to—we would dare to say pathognomonically—acute trypanosomiasis *cruzi*, of course always referring to a zone where the illness is endemic.

We base this opinion on the experience gained through nearly 25 years of observation. Neither the authors nor numerous Argentine pediatricians nor nepiologists who were consulted on the matter have ever observed an inflammatory swelling in Bichat's fat pad of any other nature.

Many doctors who know this symptom specifically from a nosological point of view, confirm our affirmations, as proved by BRAVERMAN's observations (27), because as for hypodermic chagomata concerning lipochagomata *genii* it is necessary to be aware of its existence in order to be able to find them. So much so that CRISCUOLO et al. (22) say in this respect: "The chagoma formations are present, nevertheless, in hospitals one does not come across them so frequently. This circumstance is due to the fact that the unspecialized doctor is not aware of its existence". Further on, he says: "Its discovery is proportional to the measure of the carefulness of its investigation". We quote these affirmations on

Plate II

Fig. 4. Microscopic view of the cheek of a normal seven-month-old fetus. The zone that correponds to Bichat's fat pad is formed by foam cells (immature fats, xanthomatous, fetal in type), while the neighbouring pre-parotid gland is formed by unilocular cells, typical of mature human fat ($\times 300$).

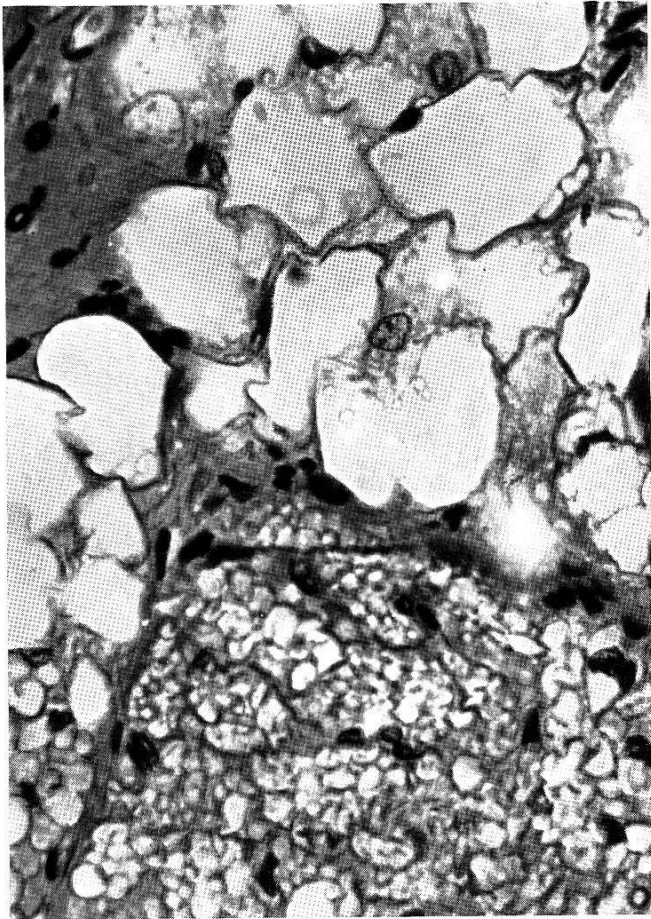
Fig. 5. Case 3. Biopsy of lipochagoma *genii* made the 15th day. Polymorphonuclear infiltration that ratifies the acute inflammatory characteristic of the lesion (Giemsa, $\times 400$).

Fig. 6. Case 3. Biopsy of lipochagoma *genii* made the 15th day. Predominant lipophagic granuloma condensation ($\times 400$).

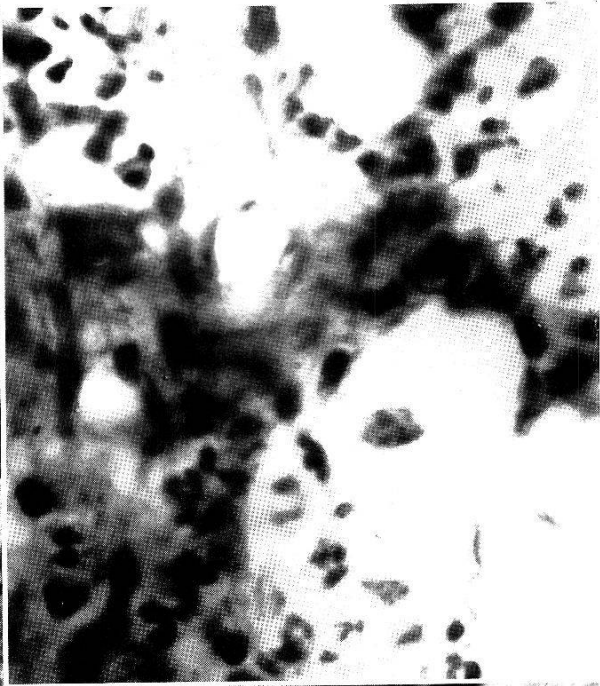
Fig. 7. Case 2. Biopsy of lipochagoma *genii*. Typical leishmania bodies in the periphery of the inflammatory focus. The nest contained more than 20 parasites ($\times 1800$).

Fig. 8. Case 3. Biopsy of lipochagoma *genii* made the 15th day. Cellular nest with abundant leishmania bodies in the panniculitis ($\times 1800$).

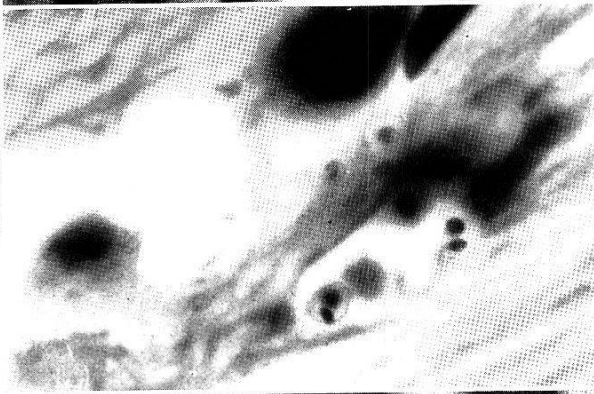
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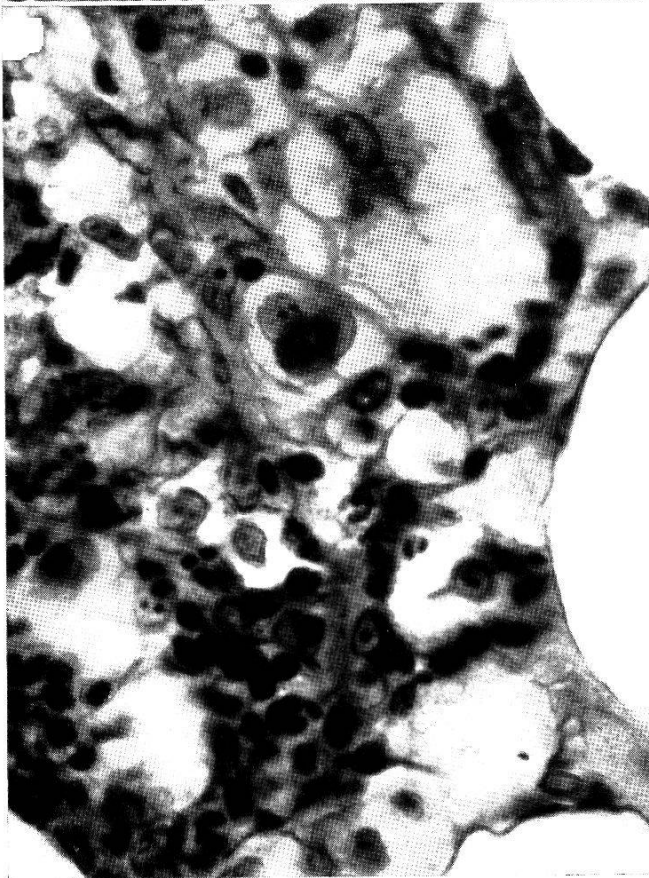
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purpose as they come from a very authorized source and are totally independant of MAZZA and his collaborators, which frees them from a presumed partiality "pro domo suo" with respect to the defence of the clinical importance of such a manifestation.

FREIRE, in his contributions on this subject, while collaborating with MAZZA in 1938 and 1940 (8, 11, 12) and in recent publications (24, 25) insists on the necessity of the manual exploration of the tegumentary swelling while searching for chagomata in children suffering from some ailment behind which trypanosomiasis cruzi can hide. BRAVERMAN (27) while working in the same endemic zone of Chagas' disease, also emphasizes this in particular when saying: "Experience has taught us to be thorough while examining the subcutaneous tissue, and to look for them systematically". This affirmation is based on the fact that the hematogenous (blood spread) chagomata can appear in any zone of the body, can be unique and can have various aspects as shown by MAZZA et al. and described in a clear synopsis by CRISCUOLO et al. (22).

The need of a systematic and careful search for chagomata in nurslings is obvious and should always be done with real interest; it shall confirm in its finding a true symptom, sometimes the only evident symptom of acute trypanosomiasis cruzi in infants (24, 25, 26).

Characteristics of the lipochagomata genii.

From a semeiologic point of view, the lipochagoma genii is a monomorphic lesion: It is an ellipsoid or bean shaped hard mass with the consistency of an acutely infarcted lymph node or a rubber ball, inclosed in the thickness of the cheek; its form resembles the form of Bichat's fat pad, very frequently of a flattened elliptical or egg-shape appearance, with its main axis on an almost vertical plane with its maximum relief at middle height, and extends between two imaginary lines, one corresponding to the zigomatic arch and the other to the extension of the corresponding buccal edge. Sometimes the lipochagomata may be seen by its relief on the facial cutaneous side, but they are always clearly noticeable

Plate III. Case 5. Acute trypanosomiasis cruzi. Biopsy of lipochagoma genii made the 25th day.

Fig. 9. Palpation of the inflammatory tumour.

Fig. 10. Leishmania bodies inside the inflammatory cytosteatonecrosis ($\times 1800$).

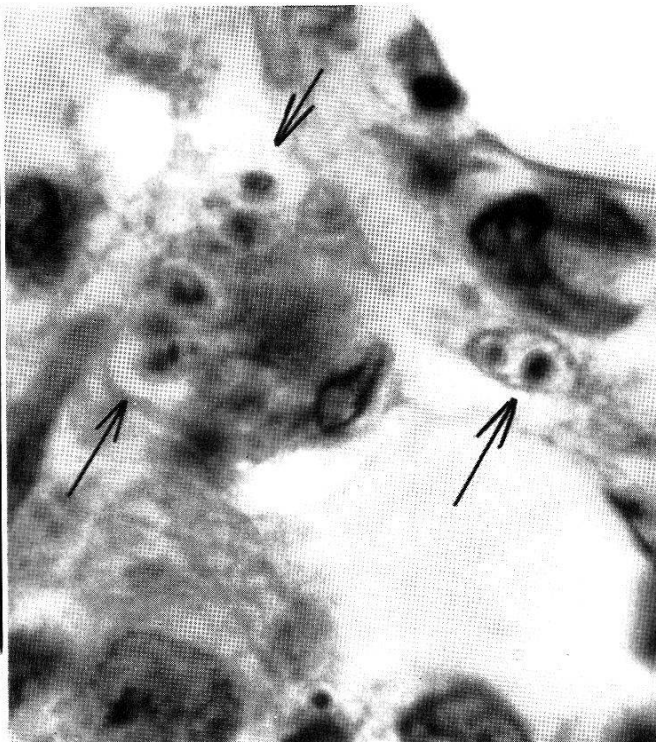
Fig. 11. Condensation of the adipose tissue and inflammatory infiltration of the hypodermis ($\times 50$).

Fig. 12. Inflammatory cytosteatonecrosis showing polymorphonuclear and mononuclear leukocytes and large lipophagic histiocytes. Mallory's stain shows connective "neofibrillogenesis" ($\times 400$).

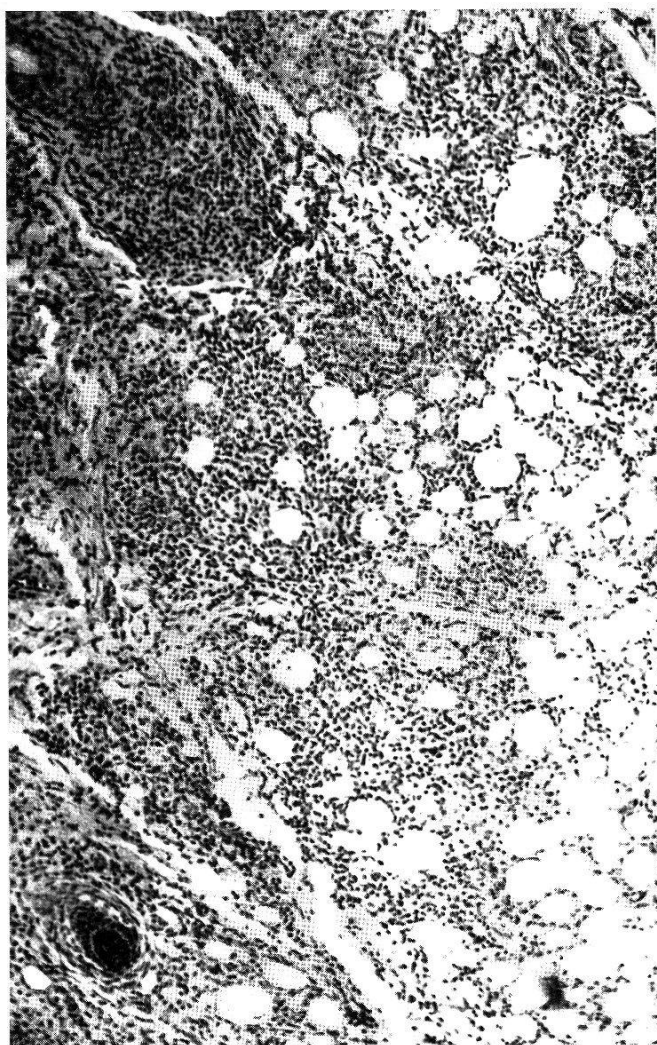
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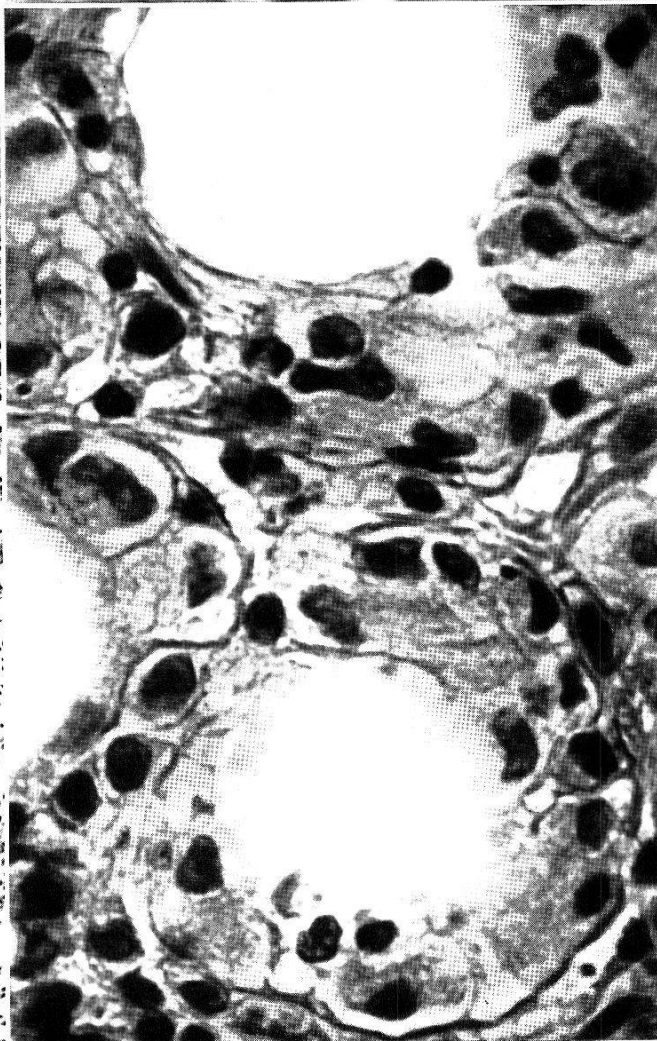
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and definable when practicing a bidigital palpation in the form of pincers, i.e. introducing the index finger inside the mouth, resting it over the mucous side of the right cheek, and locking the movement with the ball of the thumb resting on the cheek (as if stretching the thickness of the cheek in between both fingers—see Figs. 13, 14). Coming in a posterior-anterior direction while doing this bidigital palpation its presence can be immediately detected, anteriorly to the masseter muscle, if it were present; its size habitually oscillates between that of a grape, a nut or a plum. Its anterior limit usually coincides with the perimeter of the orbicular muscle. Sometimes the limit of the lipochagoma genii can not be precised through this palpation because it is confluent with the infiltration of a cutaneous inoculation chagoma, whether it can be infra-orbital or zigomatic, and also linked to the preauricular confluent lymphadenopathy which is characteristic of trypanosomiasis cruzi when the portal of entry is facial.

The lipochagomata genii are tender, sometimes very painful; often the bidigital palpation as has been mentioned produces violent crying and self-defence reactions. This fact has been frequently observed by the mothers, who apart from noticing the “excessively fat . . . as if swollen” aspect of their child, also perceive the lipochagomata directly on contact while washing or caressing them; they also mention the fact that when they breast-feed the baby, it begins to cry because the activity of the buccinator, orbicular and other muscles that take part in the sucking action, compress the lipochagoma against the facial bone structure. In some cases, children who do not present major signs of restlessness during their illness react with most violent crying crisis when the lipochagomata are compressed when palpated or while sucking.

Situation of the lipochagomata within the general classification of chagomata.

The inoculation of *Trypanosoma cruzi* produced with or without portal of entry, whether it be primary (inoculation) or secondary (lymph or blood spread) can give rise to the subcutaneous fixing of the parasites in foci that consolidate and later present a tumoural aspect. This was called *chagomata* by MAZZA and collaborators, who distinguished the following:

1. Inoculation chagomata.

There are lesions produced in the same place where the trypanosomes penetrated. They are characterized in addition to a tumoural

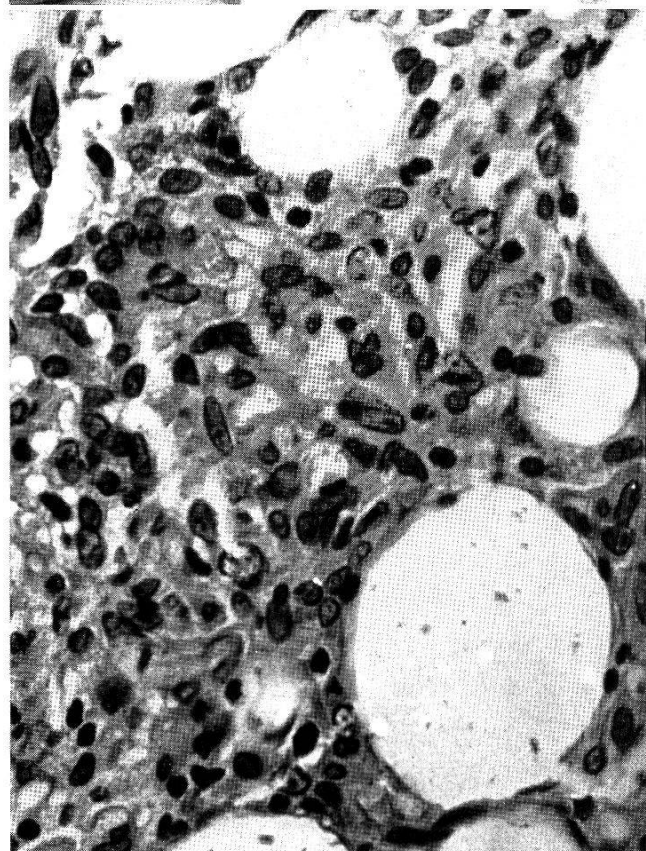
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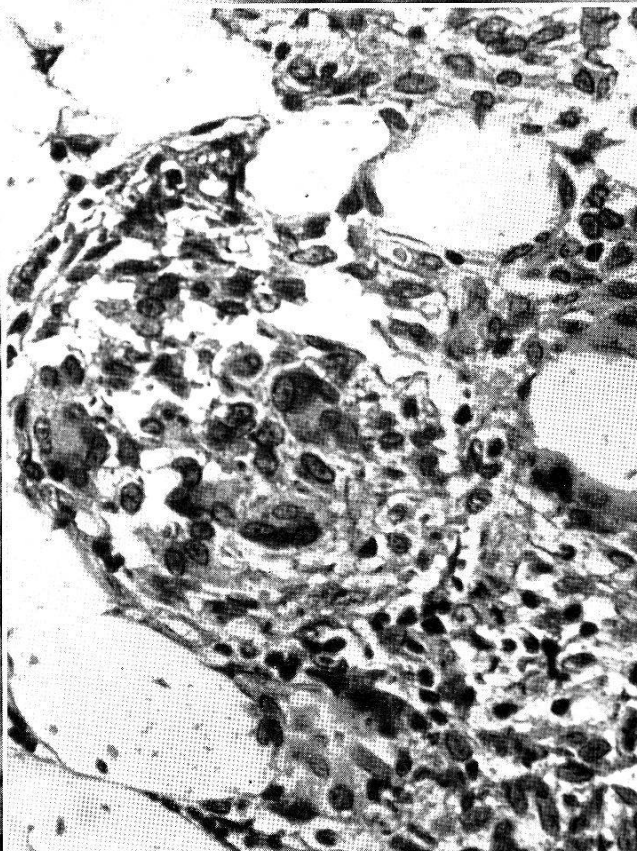


Plate IV. Case 6. Acute trypanosomiasis cruzi.

Fig. 13. Extraoral palpation of lipochagoma genii.

Fig. 14. Combined bidigital intra- and extraoral palpation of lipochagoma genii.

Fig. 15. Alternation of histiocytic infiltration with proliferation and hypertrophy of the inflammatory cytosteatonecrosis.

Fig. 16. Lipophagic granuloma including giant multinucleated cells ($\times 220$).

volume, by the firm adherence between the epidermis, dermis and the mass of the hypodermic chagoma. Pathologically it can be described as an intense erosive dermoepidermitis, pseudoulcerous, sometimes furunculous or erysipeloid, together with cytoeatonecrosis and hypodermic lipophagic granuloma, sometimes necrotic in character that can fistulize and drain as a furuncle or abscess.

2. *Metastatic chagomata.*

These are nodules which appear in proximity and simultaneously to the inoculation chagoma, as if there existed a multicentric process of cutaneous tumouroid manifestations. Microscopically an hypodermitis (panniculitis) with inflammatory cytoeatonecrosis of the subcutaneous tissue is found. Only exceptionally does the dermis participate and in this case the skin covering the nodules presents an erysipeloid or carbuncular aspect, together with epidermic adhesion and exudative distention.

3. *Hematogenous chagomata.*

These are inflamed hypodermic nodules, and appear in form of a multiple gathering. They oscillate between 8-10 which is common, up to more than 100 small tumors. They appear in absence of an inoculation chagoma or of a visible primary parasitic portal of entry, but in 1945, subsequent to this definition, MAZZA (18) equally considered as hematogenous chagomata, those inflammatory nodules that appeared in the secondary period when all the primary period phenomena of inoculation (inoculation chagoma, ophthalmyadenitic complex, etc.) have disappeared or were vanishing. MAZZA stated that when the primary period was over the concept of metastatic chagoma would not be valid as this concept involves the simultaneity with the inoculation focus. Microscopically in the hematogenous chagomata an hypodermitis (cellulitis or panniculitis) accompanied by a sometimes necrotic inflammatory cytoeatonecrosis is seen. The spreading of these lesions to the dermis is minimum and the epithelium that covers them is only exceptionally affected, and in this case always in minimum proportion.

The lipochagomata *genii* only exceptionally develop by contiguity to the facial cutaneous lesion of primary infection: in the majority of cases they have the characteristics of *hematogenous chagomata* for they appear isolated, in silent progression with no relationship to lesions of inoculation.

In many cases the lipochagomata genii are the first subcutaneous localizations, since the small patients do not exhibit definable lesions of the infection's portal of entry. Regarding this point we must, once again corroborating MAZZA and his collaborators (see i.e. the recent exposition of BRAVERMAN [27], a meritorious exponent of personal effort on the clinical investigation of trypanosomiasis cruzi) point out, as has been confirmed by our casuistry, that we cannot any longer admit the ophthalmolymphadenitic complex as a constant semeiologic manifestation of the parasitic inoculation, or as an invariable and constant sign of the first period of Chagas' disease. MAZZA and several of his collaborators demonstrated that in a majority of cases (near 70% in children under 12 years of age, and at least 40% of children over 12 years of age and adults) trypanosomiasis cruzi begins and evolves without the ophthalmolymphadenitic complex becoming apparent. This ophthalmolymphadenitic complex was prematurely and therefore erroneously transformed into a sine-qua-non manifestation of the disease. This does not mean that we wish to lessen the importance of such a manifestation that was originally described by ROMANA (3) as an "unilateral schizotrypanic conjunctivitis", to which he attached the importance of a primary and frequent sign of the beginning of Chagas' disease. When S. MAZZA insisted that the ophthalmolymphadenitic complex should not be considered as the sole and constant sign of the *Trypanosoma cruzi* infection, many people considered that he adopted such a position without any well grounded scientific reasons and proofs. But nothing better to prove what MAZZA taught as well as what we assert here in this publication than to transcribe textually what the eminent Brazilian investigator DIAS says (p. 650) in one of his important reviews of 300 cases of Chagas' disease with known initial period, field in the "Centro de Estudios de Bambui" (O Hospital, 1955, p. 647-653). "In 70 acute cases (23,3%) there were no apparent signs of portal of entry. In the cases where they were apparent, these signs had the following localization:

<i>Head:</i>	57%	Eye	146	48.7%
		Parietal region	10	
		Lip	4	
		External ear	3	
		Nose	1	
		Face	5	
		Head (outside the parietal region) . . .	2	

<i>Upper extremities: 9.3%</i>		Wrist	1
		Arm	6
		Elbow	1
		Forearm	18
		Hand	2
<i>Lower extremities: 5.7%</i>		Knee	2
		Hip	7
		Leg	8
<i>Trunk: 2%</i>		Rib cage	2
		Axilla	1
		Abdomen	1
		Chest	1
		Buttocks	1

Uncertain localizations: 8 (2.7%).

In other words, only 48%, less than half, of the 300 cases have signs in the orbital region attributable to an apparent portal of entry and almost one quarter of the cases did not present any sign at all attributable to an apparent portal of entry. The mortality in this series of cases studied by DIAS et al. was 9.17% (29 patients). There age was: less than one year, 7 cases; 1 year, 6 cases; 2 years, 4 cases; 3 and 4 years, 3 cases each; and 6, 7, 10, 14, 35 and 43 years of age, 1 case each.

This valuable statistics of DIAS confirm the experience and teachings of MAZZA, and should serve as a sufficient warning to those who consider trypanosomiasis cruzi as a simple endemiologic fancy that is recognized by a swollen eye and heals spontaneously except in rare occasions when they persist as parasitic carriers.

This manifestation that we call ophthalmolymphadenitic complex (nomination proposed by GERMAL and REDENTO BASSO to avoid eponymic conflicts on the discussion regarding designation of the primitive or secondary nature of the conjunctivitis, tenonitis and orbital cellulitis that integrate the process) is, without any doubt, one of the many symptoms, among them those described herein, as well as the lymphadenopathy and other signs (13, 15, 16, 18, 22) that are valuable for the diagnosis of trypanosomiasis cruzi, as has been proved by MAZZA, MIYARA and JÖRG (18), who reached to the diagnosis based exclusively on the presence of leishmania bodies of *Trypanosoma cruzi* in biopsies of conjunctivae when such a complex was present and no parasites could be found in the blood.

Evolution of the lipochagomata genii.

It is not possible in all cases to become aware of when the parasitic inoculation has taken place, consequently the lapse in the appearance of the lipochagomata can only be fixed in relation to the time elapsed from the appearance of the first symptoms of the illness (fever, restlessness, etc.). It is possible to mention that in our cases, the lipochagomata had reached a reasonable volume after an average of 14 days of apparent illness (minimum 5 days, maximum 28 days).

The lipochagomata genii, after reaching an inflammatory climax, recede gradually in volume and pasteboard-like tumescence. In untreated cases they disappear after an average of 20 to 25 days of evolution, although sometimes it took longer.

In cases treated with 7602 Ac Bayer, this evolution is considerably shortened and with sufficient doses it is possible to arrive at a very quick regression of the inflammation in such lipochagomata (3 to 5 days).

In some cases the lithic evolution of the inflammation of the lipochagoma is accompanied by the lessening of the volume (lipotrophy, fibrosis) and it can produce a slight retraction of the cheek; this has been shown by MAZZA, ROMAÑA & ZAMBRA (5) and by MAZZA, COSSIO & ZUCCARDI (7) although this fact is not frequently seen, according to our observations, in a contiguous lipochagoma, as in general the hematogenous genii lipochagoma disappears after a time without leaving any palpable hardness or visible deformities.

Pathology.

The microscopic examination of the biopsies of lipochagomata genii reveals an intense alteration of the deep fatty tissue of the hypodermis of the cheek, presumably the superficial part of Bichat's fat pad, because in some of the biopsies the muscular fibers of the buccinator muscle take part in the process. The alterations in the structure of the fatty tissue is evidenced by two elemental lesions: 1) An extensive inflammatory infiltration, diffuse, with condensation zones reaching a furunculoid character, composed mainly by polymorphonuclear leukocytes and in lesser quantity lymphocytes and large mononuclear cells. 2) Cytosteatonecrosis with all the typical characteristics of this alteration as described by LECENE & MOULONGUET, LEE & ADAIR (28) etc.; in two of the cases observed there was an intensive lipophagic granuloma.

As a whole, the pathological lesion of the lipochagoma genii caused by *Trypanosoma cruzi* can be defined as: Acute cellulitis of

the hypodermic adipose tissue (panniculitis), localized in Bichat's fat pad, together with cytosteatonecrosis and lipophagic granuloma.

By virtue of the intimate histologic modifications and of the cytological character of the same, it is apparent that the inflammatory infiltration and the cytosteatonecrosis are simultaneous and not consecutive. There is a clear impression that a same irritant is simultaneously responsible for both lesions.

In the five cases studied, leishmania bodies of *Trypanosoma cruzi* were found in the midst of the inflammatory tissue; not in dense accumulations or giant cells, but always dispersed and irregularly distributed in a very similar manner as showed by MAZZA, MIYARA & JÖRG (17, 18) in the biopsies of conjunctivae corresponding to ophthalymphadenitic complexes.

It is well known that one of the major problems in the microscopic identification of lesions of trypanosomiasis *cruzi* resides in the difficulty in finding leishmania bodies of *Trypanosoma cruzi* in the microscopic slides. This does not occur because of the difficulties of staining, as they are easily stained with the very common hematoxylin of Mayer, Ehrlich, Delafield and even Mallory's or iron hematoxylin (Heidenhain) in material fixed even by formaldehyde and included correctly in paraffin. It is obvious that the visibility and staining affinity improves when tissues are fixed in solutions for cytologic studies like e.g. Helly's liquid or Bouin-Allen's. The difficulty resides in the scarcity of parasites. The following examples gives an idea about it: In the mortal case of trypanosomiasis *cruzi* described by MAZZA, BASSO, BASSO & JÖRG (9) leishmania bodies were found in the myocardial lesions after having examined more than 1000 sections with immersion objective of 100 magnifications and 1.30 aperture. This task which was undertaken by 4 persons, MAZZA and JÖRG amongst them, took close on a year when realized in conjunction with the other unavoidable laboratory tasks. SALVADOR MAZZA never diagnosed Chagas' disease without first having a direct evidence of the parasite, and in this sense he never spared any effort to assure and to document by means of microphotography such a fact. This is the foundation of all his work, and the conclusions are immovable being this the proof required in all bacteriologic and parasitologic studies. MAZZA, MIYARA & JÖRG (18) were obliged, because of the scarcity of parasites, to improvise and use a microprojector similar to a trichinae detection apparatus, but of great magnifying power (see details in that publication), with which they were able to improve their findings of leishmania bodies. One must bear in mind that due to the incidence of the sections and the peculiarities of the parasitic nests, it is possible to find in one slide one, and only

one, leishmania body as is documented in Fig. 74 of the above mentioned publication (18).

The difficulty in diagnosis brought by the scarcity of leishmania bodies in the sections of tissues with presumptive inflammatory alterations due to trypanosomiasis cruzi is a barrier of considerable magnitude in the establishing of the frequency of trypanosomiasis cruzi in material of biopsies or necropsies and also to make sure if a certain lesion (such as the case of lipochagomata) can be related to Chagas' disease. That is why pathologists of recognized experience as JAFFE (19) have encountered many difficulties when trying to explain the frequency of the trypanosomic etiology in an ample series of myocarditis found in Venezuela, because the failure in finding the parasite excludes obviously the possibility of an exact diagnosis. For the pathologist it is obvious that the only proof of Chagas' disease can be given by the presence of parasites, despite the presence of lesions that cytologically and histotopographically can only be identified with trypanosomiasis cruzi.

This then forces the pathologists of all America, principally in those zones where the ecologic elements of the disease are found (naturally infected intermediate hosts, domestic infected triatomas, primitive or rural lodging) to the inexcusable necessity of making a deep search for possible infections due to *Trypanosoma cruzi* in autopsies and in cases of very suspicious lesions (myocarditis, acute non bacterial meningitis, orbital cellulitis, ophthalmadenitic complex, etc.), and the examination should be done in a large number of sections with immersion objective of numerical aperture 1.30, so as to be able to find the parasites. MAZZA, BASSO & BASSO (10); MAZZA, BASSO & BASSO (16); MAZZA, MIYARA & JÖRG (18) have diagnosed numerous cases of trypanosomiasis cruzi exclusively by finding parasites in biopsies of different altered tissues (conjunctiva of the ophthalmadenitic complex, acutely inflamed lymph nodes, chagomata, etc.).

In the case of lipochagomata the search for parasites has taken a long time and the difficulty in localizing the same in the midst of the dense inflammatory lesions, in between cellular debris and chromaffinic substances, has been such that even in already marked sections it is sometimes very troublesome to come across the leishmania bodies again.

In all the biopsies studied by us, the microscopic aspect is of a panniculitis and cytosteatonecrosis although we must mention that the proportion of inflammatory infiltration to cytosteatonecrosis is not identical in all cases. For example, in Case 2—N. B.—the aspect is predominantly inflammatory, and the polymorpho-

nuclear infiltration is so dense in some parts that it resembles a furunculoid infiltration. On the other hand, in Case 5—H. G.—a cytosteatonecrosis and lipophagic granuloma prevails ostensibly—and the infiltration is very diffuse and irregular, concentrated only around one or other necrotic adipose cell.

In the rest of the cases the proportion between both processes is approximately the same. It is very difficult to precise whether this difference is connected to the evolution of the lesion, because the exact date of onset of the disease cannot be fixed out from the very unreliable form through references made by the children's parents. Notwithstanding, the more advanced lesions of cytosteatonecrosis are found in Case 5—H. G.—, the biopsy of which was presumably done near the 25th day of evolution. Nevertheless, in Case 4—J. A.—who was examined just a few days, probably less than a week, after the onset of illness, the biopsy revealed an aspect not very different to what was found in Case 3—H. C.—and Case 6—O. L.—whose biopsies were performed on the 15th day. This study permits us to infer a certain chronology in the sequence of the lesion: initially a polymorphonuclear infiltration predominates, though cytosteatonecrosis is already evident. This cytosteatonecrosis would become accentuated in favour of the resorption of the polymorphonuclear infiltration which is evidenced by the great amount of karyolytic rests found in cases of more than 20 days of evolution.

What can be said about the differential anatomopathologic diagnosis of this lesion?

One of us (JÖRG) worked as pathologist in the Surgical Clinical Institute of the University of Buenos Aires for some years, and despite the numerous material from biopsies and necropsies that was found there, he had opportunity of examining sections of only two cases of subcutaneous cytosteatonecrosis. Both cases were taken from adults, one a subcutaneous cytosteatonecrosis of the arm, and the other cytosteatonecrosis of mammary cellular tissue; in both cases there was no inflammatory component that is so evident in all the chagomata studied by Misión de Estudios de Patología Regional Argentina, and in the lipochagomata *genii* referred to in this publication.

It would seem therefore that the inflammatory infiltration with abundant polymorphonuclear leukocytes or their karyolytic detritus is an element in the differentiation between the panniculitis with cytosteatonecrosis of the lipochagomata and the cytosteato-

necrosis of traumatic or dishormonal etiology that is fairly common.

We have not been able to compare these lesions with the lesions of generalized subcutaneous cytosteatonecrosis of the newborn because we do not possess such material, and as it was impossible to trace who can have it in Argentina.

Microscopically the lesions are not specific, and no cytologic characteristic allows us to make a diagnosis of trypanosomic cellulitis were it not for the presence of leishmania bodies of *Trypanosoma cruzi* in the focus of the lesion.

Pathogenesis of the lipochagomata.

We have no evidence of the production of lipochagomata (panniculitis and cytosteatonecrosis) in experimental animals infected with *Trypanosoma cruzi*. The only opportunity of observing a dense invasion of the subcutaneous fat was in a "pila" or chihuahua dog suffering from vitamine A deficiency, already alluded to (MAZZA & JÖRG, 4). In this material, the cytosteatonecrosis was hardly apparent, microfocal and isolated. While experimenting with animals, we have only seen traumatic cytosteatonecrosis appear in rats raised with a vitamine E and unsaturated fatty acids of the linolenic, linoleic and arachidonic etc. series deficiency. Their microscopic characteristics partially concur with those described in the cytosteatonecrosis of chagomata or lipochagomata.

It is of general knowledge that the fat of the newborn and nursing has a much higher and more unstable melting point than that of adults because of its lower olein content (MACINTOSH et al., 30). In adults, the proportion of oleic acid triglyceride oscillates between 65 and 85%, of which 19-21% corresponds to palmitic triglyceride and 5-6% to stearic triglyceride; the rest corresponds to unsaponifiable elements (cholesterol amongst them) as well as a small proportion of unsaturated fatty acids like the quoted linolenic, linoleic and arachidonic acids.

The scarcity of olein and other glycerides of unsaturated fatty acids can be probably and in part, produced by peculiarities or qualitative faults in nutrition that predisposes it to the cytosteatonecrosis, as we have observed in experimental animals.

Regarding the lipochagomata *genii* its pathogenesis is unknown. We have no references on the biochemical characteristics of the fat of Bichat's fat pad of the nursing, but we have seen in microscopic sections of 7 months foetus' that Bichat's fat pad and the surrounding facial subcutaneous adipose tissue are of somewhat different structure, and are separated by a thin collagen wall that

circumscribes Bichat's fat pad. This last structure is different because it is composed of cells of a foamy aspect (Fig. 4) and their fat is different from the neutral macrolocular fat of the common developed adipose tissue. Eventually such foamy or reticulated aspect of the cells disappears, and when birth takes place Bichat's fat pad has the typical characteristic of common subcutaneous fat.

This structural difference in the fetal Bichat's fat pad could correspond to a biochemical difference with respect to the rest of the subcutaneous fat; we only mention this as a possibility still to be proven. On the other hand we would still leave unresolved the reason of the symmetrical inflammation of both Bichat's fat pads in the lipochagomata. Could it be that the effort in sucking acts as a traumatic element on Bichat's fat pads and therefore favours the localizing process of the trypanosomes or the cytosteatonecrosis in the febrile child? This is another unanswered question that we raise.

It remains still to be determined whether nutritional characteristics in infants or mothers in the regions where these observations of lipochagomata *genii* were made, could cause a particular instability of Bichat's fat pads, that from a biochemical point of view are defined as adipose formations of late differentiation towards typical neutral fat. The lack of unsaturated fatty acids could be of great importance; also probably vitamine A (retinol) and other nutritional elements could intervene in these cases. In a strange and unique case of trypanosomiasis *cruzi* and primary lethal tuberculosis, we found in the liver the typical lesion of Kwashiorkor or weaning hypoproteinemia (JÖRG, FREIRE & BRAVERMAN, 23), which indicates that there can exist hidden nutritional disorders that are not recognized due to the difficulties encountered in making these diagnosis without the help of the delicate biochemical investigations which would confirm them.

Case histories.

Case 1.

D. Herrera is a two-year-old boy who comes from a suburb of Villa Angela. He lives in a mud hut in which many cone-nosed bugs abound. He is seen in the outpatient clinic of the Villa Angela Hospital five days after the first symptoms of the disease appeared. These began with vomiting, rejection of food, weakness and fever. As from the third day the parents noticed a manifest generalized edema, much more evident in the face which appeared deformed, and in the lower extremities, specially in the tibial region and the dorsum of the feet. On the fourth day, the mother discovered purple patches on both cheeks and disseminated over the skin of the thorax and extremities. She also perceived that each one of these corresponded to a subjacent swelling of uneven dimensions and very painful to the touch.

On admission to the Hospital, he is found to be in a good state of development and nutrition. Inspection reveals an extense and pronounced anasarca. On many parts of the body, numerous purple patches are visible. They are of irregular outline, roughly circular, whose dimensions range between 2 to 5 cm. in diameter, and when seen with a strong source of illumination lighting the area under investigation tangentially, it can be seen that these patches are in relief with regards to the plane of the skin: they have the consistency of hard rubber, with poorly defined limits, and with the dermatological characteristics of acute inflammatory nodules. These nodules, hematogenous chagomata in number of 50 or more, are disseminated on the thorax and extremities and are more densed and inflamed in the thighs, as illustrated in Fig. 3. The superficial layers of the skin are intimately linked to the nodules, and the dermis and epidermis cannot be folded over the same. The overlying skin appears red, tense and warm. On the other hand, they can be displaced over the aponeurotic plane.

The external and combined palpation of the cheeks indicates the presence of lipochagomata genii whose characteristics have been mentioned as those typical of this lesion in trypanosomiasis cruzi.

There is a fairly important spleen enlargement, a barely perceptible liver enlargement, temperature 38.3°C, pulse rhythmical 95 per minute. There is also an inguinal and femoral adenopathy. A fresh blood drop between slide and cover reveals the presence of *Trypanosoma cruzi*, thus ratifying the diagnostic suspicion of Chagas' disease.

No biopsy can be taken of the chagomata because the child's family objects. Treatment consists of 3 intramuscular injections of 0.15 gm of 3024 M, with 48 hours intervals. With this treatment the chagomata progressively diminished in size and consistency, disappearing within 14 days with no apparent sclerosis nor atrophy in the place where they had been located.

Case 2.

Nievas Barrios is a two-month-old boy. He comes from Lot No. 42, a zone of quebracho exploitation near Villa Angela. He lives with his parents and 10 brothers (all in one room) in a zinc-roofed mud hut in which cone-nosed bugs abound.

His actual illness began fifteen days before being brought to the Villa Angela Hospital. There was a moderate fever, vomiting, diarrhea (5-6 liquid evacuations daily with whitish clots). A few days later the mother discovered a hard, elongated, painful nodule behind the left ear and two grape-sized nodules, one on each cheek. Despite his illness, the child ate and slept well.

He is brought to the outpatient clinic of the Hospital by the mother on the 8th December 1946. The following is verified: satisfactory nutritional state and somatic development. He weighs 4750 gm and inspection reveals a tenuous thoraco-abdominal venous network, globular abdomen with slight umbilical hernia and a visible hypertrophy of the inguinal lymph nodes. Palpation reveals generalized lymphadenopathy on underarm and groin. External palpation reveals the relief of the lipochagomata genii; they are globular and well defined. Their size, consistence and localization can be better appreciated by bidigital palpation when introducing the index finger inside the mouth. This procedure produces reactions and crying presumably due to pain. The lipochagomata genii on the right cheek is grape-sized and the left is somewhat larger.

Temperature on examination is 37.7°C under the arm and 37.9°C in the rectum. There is enlargement of the spleen (its inferior margin is 4.5 cm.

under the rib cage border). The symptomatology and general condition of the baby is similar to a common intestinal disorder of the nursling, but the presence of the lipochagomata genii immediately led the diagnosis towards Chagas' disease. Examination of the blood with hanging drop, thick blood film method stained in Giemsa, proved the existence of great quantities of *Trypanosoma cruzi*.

Treatment consisted of 3024 M, given intramuscularly. Seven injections of 0.15 gm of active substance each were given in a lapse of twelve days. After this treatment, there was no more diarrhea, no more trypanosomes could be found in the blood (hanging drop, thick blood film) and the lipochagoma genii on the right cheek had vanished completely while on the left cheek it was still palpable and of the size of a grain of corn. He is discharged on the 14th day after admission.

Pathological findings in the biopsy of the lipochagoma genii:

There were no visible alterations in the dermis and epidermis. In the hypodermis, about 1 mm. underneath the epidermic limit, there are dispersed and irregular foci of condensed adipose tissue. This condensation is characterized by:

(1) Thickening of the thin walls separating the locules of fat by collagenous edema and by:

(2) Intense polymorphonuclear infiltration, very similar to the one observed in pyogenic panniculitis.

(3) Interstitial hyperplasia of large macronuclear cells with hypochromatophilic protoplasm, as if they were histiocytes in macrophagic function filled with lipids arising from the chemical degradation of the neutral fat of the adipose cells that are included in the inflammatory foci.

No gross cytosteatonecrosis nor lipophagic granuloma could be observed; and the general impression is that of an acute, multifocal and irregularly disseminated panniculitis that would correspond to its similar hematogeneous origin. In some foci, there is such a numerous amount of polymorphonuclear leukocytes that they resemble acute pyogenic processes, e.g. boils, perivariicose cellulitis of the legs, etc.

Case 3.

Horacio Castillo, male, three months ten days old. He lives with his parents in a room with brick walls, with plaster on the interior and zinc sheet roof, in the suburbs of Villa Angela, 1 km from the center of the town. The mother did not observe the presence of cone-nosed bugs in her house, but at present there were possibilities of finding them because she had bought an old piece of furniture wherein several examples of such bugs were found. Of the seven examples brought by the mother, three were infested by *Trypanosoma cruzi*.

His actual illness began 17 days before he came to Villa Angela's Hospital. It began with an irregular febrile state and inconstant diarrhea. These manifestations persisted, with periods of well being during approximately ten days. At this time, the mother, while bathing the child, observed a hardness situated very deeply in the right cheek, that was very painful because the child cried whenever touched in that region. On the next day the mother observed a similar hardness in the left cheek, and successively she noticed the presence of new, hard, subcutaneous nodules, one of them suprapubic and on the middle line, and two infraumbilical, each on the paraumbilical line. She takes

the child to Villa Angela's Hospital, where it is examined by one of the authors (FREIRE) and a colleague (BRAVERMAN), who found the following:

Boy in good nutritional and developmental state. Weight 5700 gm. There is a visible generalized edema of little magnitude. In the right cheek one can palpate a spheroid, nut-sized nodule, that is better perceived when using a bidigital combined palpatory method. A similar formation, of the size of a grape, is found on the left cheek. On the rest of the skin can only be found nodules already encountered by the mother: two symmetrical, ovoid shaped, nut-sized nodules below the umbilicus, and a third immediately above the pubic arch. There is no change in colour of the skin, and no perceptable external swelling. They are of the consistency of cartilage and scarcely displaced. They extend in depth up to the aponeurosis and are very painful when palpated. There is also painful enlargement of the liver and spleen, and the inferior limit of the last mentioned is 3-4 cm below the rib cage,

The presence of lipochagomata led us towards the diagnosis of trypanosomiasis cruzi and in effect, the examination of the blood in fresh hanging drop and in thick blood films stained with Giemsa's, were positive as two adult forms of *Trypanosoma cruzi* are found. Later, Prof. SALVADOR MAZZA, using the same blood examination method, confirmed the diagnosis when he found 28 *Trypanosoma cruzi* (14th November 1946). Biopsies which included epidermis, dermis and hypodermis, were taken of the right lipochagoma genii and of the right paraumbilical chagoma, and the results are described further on.

Evolution.

14th of February: Treatment is started with 0.15 gm of 3024 M in 5 c.c. of distilled water (intramuscular injection).

15th of February: Temperature 37.8°C at 17.00 hours. Three *Trypanosoma cruzi* are found in blood with the thick blood film method (Prof. MAZZA).

17th of February: Second injection of 0.15 gm of 3024 M is given. Underarm temperature 37.2°C. There is an appreciable reduction in size of the liver, spleen and right lipochagoma. Diarrhea is diminishing. One *Trypanosoma cruzi* is found in the blood through thick film (Prof. MAZZA).

18th of February: Third injection of 0.15 gm of 3024 M is given. The decrease in size of the right lipochagoma is very evident, while the left lipochagoma and abdominal chagomata do not decrease in like manner. New small bean sized chagomata appear in inguino-femoral area. No more *Trypanosoma cruzi* are found in blood using the same investigation method described above (Prof. MAZZA). 4th injection of 0.15 gm 3024 M is given.

20th of February: Fifth injection of 0.15 gm of 3024 M is given. The tumours are stationary and the evolution is delayed compared with the evolution of cases treated with 7602 Ac Bayer.

23rd of February: Sixth injection of 0.15 gm of 3024 M is given. Underarm temperature 37°C. Pulse 109 per minute. There is no more diarrhea and the spleen is barely palpable.

26th of February: Seventh injection of 0.15 gm of 3024 M is given. There is no more temperature nor diarrhea. The right lipochagoma genii and the inguino-femoral-suprapubic chagomata have disappeared. The left lipochagoma genii has the size of a corn grain. The umbilical chagomata are reduced in size and are soft. The general condition of the patient (nutrition, sensorium etc.) is excellent.

4th of March: All chagomata have disappeared completely. The inferior limit of the spleen is still palpable 1 cm below the rib cage. He is discharged from Hospital.

Pathological findings in the biopsy of the lipochagoma genii.

The epidermis had visible alterations. The dermis had small, isolated infiltrations. All the subcutaneous adipose tissue was deeply altered in a diffuse form and only small areas kept their normal structure. These alterations consisted on condensation and modifications in structure of the adipose tissue by: Thickening of the walls that separate the locules of fat because of a) Infiltration by polymorphonuclear leukocytes and b) Foci of cytosteatonecrosis and lipophagic granuloma.

In this case the foci of cytosteatonecrosis are roughly evident together with the polymorphonuclear infiltration by a) Shrinking of the adipose cells with deep modifications in the normal staining of the fat; b) Apparition around the altered cells of large cells of clear protoplasm, with amblychromatic nuclei with the same characteristics described by MALLORY, MAXIMOW and LEE & ADAIR as macrophages of the detritus of the degradation of the neutral fat. Also found were several elements of the histiocytic type, fibroblastic type and even large mononuclears similar to polyblasts or monocytes.

In this case the process can be defined as an acute, multifocal, confluent panniculitis with cytosteatonecrosis and lipophagic granuloma. The areas where the polymorphonuclear infiltration is more intense coincides with the areas of cytosteatonecrosis, and in some cases it is so dense that it looks like infiltrations due to pyogenic bacteria.

Case 4.

Pilar Silva; sex: male; age: two years; from Cabeza del Tigre (12-15 km South of Santa Sylvia, Province Chaco). He lives with his parents in a mud hut where many cone-nosed bugs can be found. From ten samples of these bugs, five were found to be infested with *Trypanosoma cruzi*.

The illness began fifteen days before he was seen by us with fever, food rejection, nausea, vomiting and progressive weakness. Four days after this onset, the mother noticed a general swelling in the boy, specially in the face, legs and dorsum of the hands and feet. This increases progressively until some days later she noticed the presence of hard nodules, dispersed all over the surface of the body. With these manifestations he is brought to the consulting room of one of the authors (FREIRE) on November 4th, 1947. He is found properly developed and in apparent good nutritional state despite the evident deformity caused by the intense swelling. There is a very intense generalized edema, specially on the thighs, legs and feet. This causes a maximum distension of the skin. The face appears bloated, giving the child a grotesque appearance. The edema is hard, elastic and does not pit upon pressure.

In several areas of the cutaneous surface, numerous projecting nodules are visible, over which the skin has acquired a darker pigmentation compared with the surrounding tegument. This can be seen much better with a strong source of illumination lighting the area under investigation tangentially. In the left supraspinatus region, a tumorous mass in the process of necrotic softening and on the verge of spontaneous opening is observed.

Palpation confirms the existence of such intracutaneous nodules, they are very abundant, about 200, and are extended all over the body, from head to toes. The biggest nodules have the size of a hen's egg, of spheroid form, hard, of cartilaginous consistency. Most of these nodules are completely adhered to the dermo-epidermic portion of the skin, as if making one single element with it, and it is quite impossible to fold the skin over itself. These nodules extend well into the subcutaneous tissue and in general, the lateral displacement over

the aponeurosis of the superficial muscles is possible only in a limited way. In the supraspinatus region, one of the nodules fluctuates due to its necrotic softening.

A spheroid tumour, of the size of a big grape on the right, and of a nut on the left, is palpated in both cheeks. They are hard, painful and attached to the facial skin.

Underarm temperature is 36.4°C, the spleen is palpated 4 cm below the rib cage, slight liver enlargement and generalized lymphadenopathy can be perceived. After the diagnosis of Chagas' disease was made, a fresh blood examination was made, and four *Trypanosoma cruzi* were quickly found. This was later corroborated by the finding of twelve *Trypanosoma cruzi* in thick blood film stained with Giemsa's.

The visible aspect of the disease was documented both in cinema and photograph (Fig. 3).

It was impossible to keep the child in hospital for a better study and treatment, neither could a biopsy be performed due to the opposition of the parents.

He is examined again ten days later (November 15th, 1947) and, although the generalized edema is much reduced, his pulse is 112 per minute with no alterations. The chagomata have diminished considerably in size, they are of irregular shape and less painful than before. In several places the overlying skin presents some pigmentation of decreasing perimeter. Two chagomata in the back and one in the deltoid region have softened up and evacuated. The spleen enlargement is also much reduced. The right lipochagoma *genii* is barely perceptible and the left lipochagoma *genii* has been reduced to half of its original size. The blood examination reveals very few *Trypanosoma cruzi*, and only after exhaustive search in fresh hanging blood drop.

It is not possible to continue the study of this case, nor its evolution, due to the fact that he is not brought again nor can his address be localized.

Case 5.

José Abayay, sex: male; age: three months, from Santa Sylvina, town located 50 km South East of Villa Angela. He is brought by the mother on September 26th, 1950. The illness began sometime before with fever and a catarrhal tracheobronchitis. Three days ago the mother noticed a subcutaneous hardness in the right cheek while kissing him. The child cried whenever kissed on that cheek. He is admitted in Hospital together with the mother.

The boy is found in an excellent nutritional state, weight 6100 gm. Palpation of the right cheek reveals immediately the tumourous mass to which the mother referred. Its form and size is similar to a nut, slightly flattened. It is not possible to fold the overlying skin over the nodule, and even the slightest palpatory manoeuvre is extremely painful as the child defends himself and cries violently. Bidigital palpation reveals a hard, fixed, inflammatory tumour, whose perimeter and relations coincide with those of Bichat's fat pad.

This symptomatology led us immediately to suspect that this lesion could well be a lipochagoma and that the boy was suffering from trypanosomiasis *cruzi* or Chagas' disease.

We also found liver and spleen enlargement (inferior limit, 2 cm below the rib cage), generalized lymphadenopathy and symptoms of catarrhal bronchitis. The microscopic examination of the blood confirmed the presumptive diagnosis (three *Trypanosoma cruzi* were found in ordinary fresh blood drops and eight *Trypanosoma cruzi* in thick blood films stained with Giemsa's. Biopsy is taken of the lipochagoma and also photographs and films (Fig. 10).

On the same day treatment is started with 7602 Ac Bayer, 0.15 gm injected intramuscularly. These doses are repeated on September 28th, September 30th, October 2nd, and October 4th, 1950, totalling 750 milligrams, that means to say 123 milligrams per kg of weight. After the third injection, no more trypanosomes could be found in blood. On October 4th, 1950, a stitch is withdrawn from the lesion of the biopsy of the lipochagoma. It has healed by first intention and the size of the lipochagoma has been reduced to that of a bean.

He leaves the Hospital on October 5th and is seen one week later. He has no temperature and the lipochagoma has faded away. There is still a very slight spleen enlargement and a micropolyadenopathy.

Pathological findings in the biopsy of the lipochagoma genii. It included epidermis, dermis and subcutaneous adipose tissue. The epidermis is undamaged. Dermis is infiltrated in a diffuse form by a mass where large mononuclear cells predominate and where lymphocytes and granulocytes can also be found although not so abundantly. This infiltration is so dense in the limit between dermis and subcutaneous adipose tissue that it resembles a leukemic reaction. The adipose tissue is extensively and intensely infiltrated and has the characteristics of an acute panniculitis. In some areas, but not in a generalized nor confluent form, foci of cytotesteatonecrosis with lipophagic granuloma can be seen. There is no gross cytolysis nor intensive macrophagia that is seen normally in similar lesions.

Case 6.

Hugo Gimenez, age: six months; sex: male, from 8 km East of Santa Sylvína. He lives with his parents in a hut with walls made of mud bricks, ceiling made of galvanized steel plates in some parts and of a combination of straw and earth in others. Many cone-nosed bugs could be found in its interior.

On the 1st of October, twenty days before he was brought in consultation to this Hospital, the parents of the child noticed when wakening him up in the morning that the eyelids of the left eye were intensively red, edematous and stuck with a mucopurulent secretion, the edema increasing in successive days. A doctor was therefore called on to see the patient, who after examination suspected Chagas' disease, but only prescribed local treatment with sulphonamides and an emollient collyrium.

On October 21st, 1950, he is brought to Villa Angela's Hospital. Inspection and palpation of the ocular lesion and its lymphadenopathy confirmed the initial evidence that this process had not the characteristics of a primary ocular process, but that of an ophthalmolymphadenitic complex due to trypanosomiasis cruzi, as is confirmed by the finding of the following symptoms: fever, tachycardia (higher to that presumed due to thermic elevation), inflammatory enlargement of the liver, and particularly by the presence of bilateral lipochagomata genii of the size of a large bean. This diagnosis was later ratified by the presence of ten *Trypanosoma cruzi* in a blood examination (hanging drop, thick blood film stained with Giemsa's).

Six days later he is admitted to Hospital because of a deteriorated condition. The same amount of *Trypanosoma cruzi* persists in blood (same blood investigation method), but the lipochagomata have increased in size reaching the volume of a nut. They are very hard, very well limited by palpation, situated at the place that typically corresponds to what used to be Bichat's fat pad. Palpation, even done very cautiously, becomes very painful to the patient resulting in violent crisis of crying. The photograph (Fig. 14) shows

the volume and the form obstacle that the hardness of the lipochagomata opposes to the bidigital palpation.

Bidigital palpation (intraorally and extraorally, Fig. 14) allows us to appreciate quite easily and precisely the volume, hardness, location and relationship of the lipochagoma genii. An external biopsy was taken of the lipochagoma; it healed by first intention and a small stitch was removed four days later.

He is treated with three intramuscular injections of 0.15 gm of 7602 Ac Bayer each. He is given one injection every other day; totalling three injections. His condition improves and he is discharged from Hospital. On November 16th, 1950, he is seen again and there is a completely negative symptomatology, including no lipochagomata, and a blood examination is negative as no parasites are found.

Pathological findings in the biopsy of the lipochagoma genii. There is a deep alteration in the adipose tissue, with areas of condensation due to 1) Predominance of a cellular hyperplastic aspect; it has the characteristics of a cytosteatonecrosis and lipophagic granuloma with abundance of giant multinucleated cells of varied forms and sizes. There is also a deep alteration in the structure of the fat, deformation of loculi and cellular condensation islets and some bands of collagen neoformations. 2) Together with the areas of condensation described above there is a polymorphonuclear leukocyte infiltration and on a lesser scale monocytic and lymphocytic infiltration. This leukocytic infiltration is diffuse and it does not concentrate in any spot, not even around the altered fat locules.

In brief, there is an intense inflammatory cytosteatonecrosis with a lipophagic granuloma that is very rich in giant cells. The inflammatory infiltration is only moderate.

Case 7.

Otilia Lopez, sex: female; age: two months, from nearby to Ñandubay. She lives with her parents in a straw-roofed mud hut, where cone-nosed bugs abound.

Halfway through December, that is fifteen days before she is brought to Hospital, the mother noticed the following symptoms: fever, intense and continuous crying, generalized contractions and stiffening of the body, retraction of the head and arching of the back. She frequently vomited the maternal milk. After four days, a dry cough of medium intensity appeared. It was continuous, obstinate and stubborn. As this symptomatology was worsening, she is seen by a doctor, who does not reach to any diagnosis, and prescribes drops of mercurial lactate as treatment.

On the third of January 1951 the mother, while washing the baby, noticed the presence of a grape-shaped, hard, painful mass in the right cheek. On the next day she noticed the presence of a similar nodule in the left cheek. On January 6th, 1951, the girl is admitted to Villa Angela's Hospital, for proper examination and treatment. Her nutritional and developmental state is normal. No visible anormalities appear to inspection. There is temperature (38.2°C underarm) and the pulse is 124 per minute.

Palpation of both cheeks reveals the presence of hard, ovoid well-limited nodules. The nodule in the right cheek is slightly bigger than the one on the left; its size being comparable to a big grape. The overlying skin cannot be folded over the nodules and palpation is apparently very painful. When palpating, no cutaneous infiltrations nor hardness can be appreciated. There is a moderate enlargement of both spleen and liver, generalized lymphadenopathy that is specially evident in the inguino-femoral and axillar groups.

The presence of the typical lipochagomata genii immediately suggested the diagnosis of trypanosomiasis cruzi, diagnosis that is later confirmed by the finding of three *Trypanosoma cruzi* in the blood examination (ordinary microscopic fresh blood examination).

A cutaneous biopsy of the right lipochagoma genii is taken, the impression being that its consistency is that of lard, because after the resection is made, there remains a small cavity that does not collapse, as if removed with a hollow-punch. Despite this, the lesion heals by first intention, without leaving a scar.

She is discharged from Hospital one week later, after having received four injections of 0.15 gm each of 3024 M.

Pathological findings in the biopsy of the lipochagoma genii. A dense picture of alterations is seen, and can already be visualized in the deep part of the dermis, where striated muscle bundles are intensely infiltrated with polymorphonuclear leukocytes and lymphocytes, although with no catabiotic alterations of such fibers.

The adipose tissue of the hypodermis is found deeply altered due to a cellular condensation that substitutes the normal reticulated aspect of subcutaneous fat. This condensation is seen occupying large areas or islets, many of them confluent with one another, and the following pathological elements can be found in them: Typical cellular elements that characterize the cyto-steatonecrosis and its immediate sequel, the lipophagic granuloma. In this case the lipophagic granuloma is formed mainly by the presence of great amounts of huge histiocytes in macrophagic function, and also by the usual multinucleated cells that are seen in cyto-steatonecrosis. The cellular accumulations include many confluent epithelioid cells, thus resembling in many a way a phthisic granuloma.

All the cellular condensation in the adipose tissue is found extensively infiltrated by leukocytes, apparently in a proportional way regarding polymorphonuclears, lymphocytes and mononuclear cells (whether they are hematic monocytes or polyblasts of local origin).

Summing up we can say there is a subacute panniculitis with cyto-steatonecrosis, lipophagia and infiltration.

Epicritic considerations.

In future studies, it will be equally necessary to establish the relationship or the precise difference between two processes: a) Acute trypanosomiasis cruzi with multiple chagomata (called by CRISCUOLO et al. [22], *chagomatose* form; 10% of all the cases of the disease seen by them have showed this form), b) Classical multifocal subcutaneous cyto-steatonecrosis (non trypanosomic) whether observed in Argentina or in other countries. Regarding this last process we must bear in mind very particularly the subcutaneous cyto-steatonecrosis of the newborn and nurslings that is also called sclerema or scleredema. In effect, although a form of cyto-steatonecrosis, probably related by its etiology to a possible "fetal dystrophy" of the adipose tissue and also to possible trauma during childbirth (prolonged parturition, internal versions, re-

animation manoeuvres, tough and forceful handling of the subcutaneous tissue) is well known world over; cases have also been described of late cytosteatonecrosis in infants of up to one year of age or more, and therefore its etiology can not be attributed to intra-uterine or post-partum trauma, as was the case in the previous description. This form, dystrophic, late, subcutaneous cytosteatonecrosis in infants, can be confused with the chagomatose form of trypanosomiasis cruzi.

It is very plausible that in Argentina and probably other countries where trypanosomiasis cruzi is endemic, there occur both processes together, that means that there is a subcutaneous cytosteatonecrosis in infants, of indubitable dystrophic origin, liberated by trauma or other factors, whether precocious (of the newborn) or late (up to one year of age), together with a very alike, multifocal, confluent lesion, not of dystrophic nor traumatic etiology but corresponding to the initial phase (multiple chagomata) of Chagas' disease.

It is very true that the chagomata and lipochagomata *genii* attract attention because of their inflammatory character, their apparition together with temperature, with liver and spleen enlargement (moderately or scarcely perceptible), and in absence of other clinical elements that would suggest a different diagnosis. The chagomata and lipochagomata *genii* are big nodules, situated deeply in the hypodermis but confluent with the dermis, and therefore the superficial planes can not be folded or displaced over the nodules. This characteristic is opposed to the frequently found micronodular, miliary or pisiform characteristic of the cytosteatonecrosis of the newborn and to the so-called sclerema, that presents itself in plates of irregular extensions, but only exceptionally in the form of perfectly circumscribed nodules. In the cytosteatonecrosis of the newborn, the center of the nodules liquefies, and whenever an incision is performed, a small quantity of altered fat escapes. In contrast to this, the cytosteatonecrosis of the chagomata is accompanied by a lard-like condensation, and the incision and removal of part of the nodules when a biopsy is taken produce a hollow excavated space of rigid walls, that does not collapse and would seem to have been punched by a hollow-punch. Also, the cytosteatonecrosis of the chagomata is microscopically an acute inflammatory process, with polymorphonuclear leukocytic infiltration and not an exclusive lipophagic process. Occasionally the chagomata form abscesses and the liquid that drains is a mixture of fat, pus and great amounts of polymorphonuclear leukocytes. We did not notice the presence of germs in the slides (direct extensions) although no cultures were taken.

So as to make sure the differential diagnosis, we have initiated an inquiry among Argentine pediatricians and dermatologists, and more than two hundred letters were sent to them. The number of replies has been scarce so that the authors feel not able to state any definite conclusions, but the leading pediatricians, J. P. GARAHAN, F. DE ELZALDE, R. P. BERANGER, D. AGUILAR GIRALDES, O. TRACCHIA and the dermatologists L. E. PIERINI and M. QUIROGA have all informed us that they have never observed cases whose symptomatology could be confused with, or similar to, our descriptions concerning multiple chagomata or lipochagomata genii. We hope to be able to extend this study.

A tendency to consider the study of clinical investigation of trypanosomiasis cruzi as already exhausted exists among some groups of investigators. They consider that the clinical investigation would rely exclusively on sectors such as epidemiology, sanitary census, sanitary geography, etc. What has been said in this publication on lipochagomata genii illustrates the existence of certain aspects of this illness that still deserve special attention, and whose deeper and more precise investigation will allow an easier and surer diagnosis, and therefore a clearer differentiation from other diseases. The advance in knowledge of the clinical details of Chagas' disease with more precise methods of investigation will permit a more exact and thorough knowledge of its evolution and will contribute with more concrete and objective elements towards its therapy.

In this manner it will be possible to obtain a clearer picture of Chagas' disease as a nosologic entity in a more rational form, and all the necessary information for its easier diagnosis, imperative prophylaxis, eradication and adequate treatment will be in reach of all American doctors.

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Résumé

Cette étude est consacrée à une manifestation clinique de la trypanosomiasis américaine ou maladie de Chagas. Une tuméfaction aiguë avec cytostéatonecrose de la boule grasseuse de Bichat constitue en effet un signe sémiologique important. Cette lésion a été dénommée lipochagomata genii par MAZZA et FREIRE en 1940 et ce mémoire en étudie la pathologie.

L'importance des lipochagomes de la joue est due au fait qu'ils peuvent constituer le seul symptôme de trypanosomiasis américaine, et peut-être pathognomonique en région d'endémie, à côté de signes peu spécifiques tels que fièvre, anorexie, vomissements, diarrhée, catarrhe trachéobronchial, etc., lorsque les autres symptômes caractéristiques de la maladie, en particulier le complexe ophtalmolymphadénique (signe de Romana) font défaut.

Les lipochagomes peuvent être vus aisément, mais la palpation bidigitale extra- et intraorale, en contournant ainsi la boule de Bichat entre le pouce et l'index, permet d'en apprécier la consistance et l'importance comme le mon-

trent les figures correspondantes (Fig. 13, 14). Ils peuvent avoir la taille d'un grain de raisin à celle d'une noix, et être ovoïdes ou réniformes. Leur consistance est élastique, ils sont sensibles et la pression entraîne des cris chez l'enfant. Leur développement maximum correspond au 15^e jour de la maladie; ils s'effacent au bout d'un mois ou plus rapidement encore si l'on traite les enfants par les dérivés aminoquinaldil.

Sept cas cliniques de la maladie de Chagas sont présentés, qui tous montraient des lipochagomes de la joue. Dans 4 cas, le lipochagome constituait le seul symptôme caractéristique. 5 cas ont été biopsiés par voie externe, la plaie a guéri en un premier temps sans laisser de cicatrice.

L'étude histologique pratiquée dans tous les cas a chaque fois permis d'observer une inflammation aiguë du tissu sous-cutané donc une panniculite avec infiltration plus ou moins importante par des polynucléaires. Dans certains cas cet exsudat peut être massif et prendre un aspect furonculoïde dans les couches les plus superficielles du derme. Dans un cas il y avait une myosite du muscle buccinateur.

Dans toutes les biopsies de lipochagome de la joue il a été possible de reconnaître des corps leishmanoïdes de *Trypanosoma cruzi* et de confirmer ainsi la nature parasitaire de cette inflammation. Les auteurs discutent finalement tous les facteurs pathogéniques pouvant conduire à la stéatonécrose d'une zone aussi limitée. Un facteur nutritionnel est évoqué dans la genèse des lipochagomes sous-cutanés de la trypanosomiase cruzi.

Zusammenfassung

Eine klinische Manifestation der amerikanischen Trypanosomiase oder Chagas-Krankheit bei Kindern im Alter unter 3 Jahren wird beschrieben. Sie besteht in einer akuten Anschwellung mit Cytosteatonekrose des Bichat's Fett-pfropfens. Dieses Krankheitsbild wurde von MAZZA und FREIRE 1940 *Lipochagomata genii* benannt, und die vorliegende Arbeit bespricht dessen Pathologie.

Die *Lipochagomata* in den Wangen haben besondere Bedeutung, da sie neben völlig unspezifischen Anzeichen, wie Fieber, Erbrechen, Appetitlosigkeit, Diarrhoe, Tracheobronchial-Katarrh, das einzige sichtbare Symptom der amerikanischen Trypanosomiase (vielleicht pathognomonisch, in der endemischen Zone, wo diese Beobachtungen gemacht wurden) sein können. Andere für diese Krankheit charakteristische Symptome, wie vor allem der ophthalmolymphadenitische Komplex, können hingegen völlig fehlen.

Die *Lipochagomata* sind im Gesicht leicht zu erkennen, und ihre Ausdehnung und Konsistenz kann durch eine bidigitale intra- und extraorale Palpation genau festgestellt werden (s. Abb. 13, 14). Ihre Größe variiert zwischen derjenigen einer Weinbeere und derjenigen einer Nuß; sie sind ellipsen- oder nierenförmig und von elastischer Konsistenz. Sie sind sehr schmerzhaft, das Betasten löst immer heftiges Weinen und Abwehrbewegungen bei den Kindern aus. Nach etwa 15 Tagen erreicht die Schwellung ihren Höhepunkt, klingt jedoch nach einem Monat vollständig ab oder verschwindet noch rascher bei einer Behandlung mit einem Aminoquinaldil-Derivat.

7 Krankengeschichten von *Lipochagomata genii* werden beschrieben. Bei 4 Fällen waren die *Lipochagomata* in den Wangen das einzige charakteristische Symptom. In 5 Fällen wurde eine Biopsie von außen den Wangen entnommen, jedesmal heilte die Wunde rasch ab, ohne eine Narbe zu hinterlassen.

Die histologische Untersuchung ergab immer eine akute Entzündung des subcutanen Gewebes (Panniculitis) mit einer mehr oder weniger starken Infiltration von Polynucleotiden. In gewissen Fällen war die Infiltration sehr tief

und dicht und nahm in den obersten Hautschichten einen furunkulösen Charakter an. In einem Fall wurde außerdem noch eine Myositis des Buccinators gefunden.

In allen Biopsien war es möglich, Leishmanien von *Trypanosoma cruzi* zu finden und damit die parasitäre Ursache der Entzündung zu bestätigen. Zum Schluß wird versucht, die pathogenen Faktoren zu erfassen, die zu einer Cyto-
steatonekrose einer so eng begrenzten Zone führen. Ein Zusammenhang mit der Ernährungsweise wird vermutet.
