Histology of measles eruption

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Papers dealing with the histology of measles eruption are notoriously scarce, as Catrin noticed since 1891.

Changes in the lungs, lymph nodes, spleen, bone-marrow, liver and adrenals are described besides those found in the skin (Ciaccio, 1910, Miller, 1945).

The interest of the pathologists was lately concentrated in the finding of multinucleate giant cells in the lymph tissue along the digestive tract, specially the tonsils and vermiform appendix, as well as the spleen, thymus and lymph-nodes of the abdomen, which are regarded as pathognomonic in the prodromal stage of the disease.

Such cells have been called Warthin-Finkeldey giant-cells (S. Semsroth, 1939, Corbett, 1943, Simon & Ballon, 1948), and are considered by some authors (Gordon & Knighton, 1941) as a more sensitive indication of experimental measles than are clinical manifestations.

The cytoplasmatic granules formerly identified by Lipschütz, (1928, 1929 a e b, 1930) to abnormal central bodies in histiocytes, endothelium of blood vessels and epithelial cells have lost apparently the great interest they deserved when first demonstrated in the cutaneous lesions of measles. As such structures were formerly studied by Mallory & Medlar (1920), the cells in which they are found will be called in this paper Mallory-Medlar-Lipschütz' cells.

The opinion is divided as regards the changes present in the skin in measles eruption. Epidermal changes are mentioned in the old literature (Catrin, 1890 Ewing, 1909). Some views found in Ewing's paper such as the bacterial eiology of measles, the similarity of cytoplasmic inclusions in measles and small-pox, the absence of uniformity in the changes themselves and the possibility of the clinical picture of measles be induced by several etiologic agents were not correct, and this brought naturally some discredit to it.

Epidermal changes preceding those of the corium were described also by Abramow (1921), but other lesions referred by him such as the presence of cells containing two nuclei, and specially the strange catarhal inflammation of the epidermis which opens in the dermis did not receive confirmation.

The informations given by Kyrlé (1927) about epidermal changes in measles are scanty. Referring to his plate he says: — "Im Schnitt
durch einen Morbillenfleck (Abb. 10) ist ausschliesslich der Papillarkörper Sitz der Läsion, akut entzündliche Erscheinungen geringsten Grades stellen das Wesen derselben dar. Irgendwelche spezifische Note trägt die Alteration nicht. Im Bereich der Oberhaut mikroskopisch normale Verhältnisse.” (S. 28).

The pulmonary changes in measles ought to be regarded under an unexpected angle if confirmed the work of Pinkerton, Smiley &Anderson (1945). In sections from 2 of 6 fatal cases of clinically typical measles they found an identical picture of giant cell pneumonia with nuclear and cytoplasmic inclusions. They suggest the following interpretation for their observations: (1) that giant cell pneumonia is a lesion caused by the measles virus, which may occur with or without the usual clinical manifestations of measles and (2) that giant cell pneumonia is caused by another virus which may act independently or in association with the measles virus.

According to Mallory & Medlar (1920), sections from the earliest lesions show changes both in the epidermis and in the corium. The lesion in the epidermis are chiefly of two kinds, exudative and retrograde. The exudation consists of serum and of endothelial leucocytes. The serum leads to swelling and vacuolation of the epithelial cells and to the formation of minute vesicles beneath the cornified layer. Minute pustules some of which are already beginning to dry up are found in the early stages. The retrograde changes consist most noticeably of necrosis of epithelial cells, both singly and in small clumps. In older lesions the exudative process in the epidermis is less marked and soon ceases, and the pustules dry up and form thickened plaques in and beneath the cornified layer (mistaken for hyperkeratosis by Ewing). “The changes in the epidermis show best in the earliest lesions obtained, that is, twelve to twenty four hours after the appearance of the exanthema; and even then many of them are already beginning to dry up. This time relation would seem to suggest that they are primary, and those in the corium secondary to them but this view is probably not correct for the following reasons: The cell changes in the epidermis are not present over all the skin lesions; when present they are usually multiple over each maculo-papule; they do not occur without the changes in the corium. In other words, they are probably secondary to the inflammatory process in the corium. The lesions starts in the corium, in and around the superficial blood vessels.”

MATERIAL

Small pieces of skin were removed from patients in which the measles eruption was well developed, fixed in 10 per cent solution of formalin and Zenker's fluid, embedded in paraffin and the sections stained by the usual methods.

The material was diligently collected by late Dr. J. de Castro Teixeira in the years 1931-32 when both of us were Assistents of late Prof. Carlos Chagas, the patients being admitted to the Hospital São Fran-
cisco de Assis, Rio de Janeiro except one which was admitted to Hospital Oswaldo Cruz (now Evandro Chagas).

The first results of their study were published at the time (Torres & Teixeira, 1932 a, b and c).

A recent revision of such material lead us to some conclusions not reached before when Dr. J. de Castro Teixeira was alive, and that is the reason why this paper is not written in collaboration.

REPORT OF CASES

Case 3364: — N. F., a colored girl, 3 years old, was admitted to the Hospital São Francisco de Assis on January 23, 1932.

The physical examination revealed fever, reddening of the conjunctivae, coryza, angina, and Koplik's spots. The typical macular measles rash was first noticed on January 27, being well developed the following day.

The subsequent course was that of a typical measles case.

Histologic examination (10 hours after the onset of the eruption): — The stained sections of the specimen measure 3 x 1 mm.

The changes interest only the epidermis. Circumscribed areas of epidermal cells with cloudy swelling are associated to intercellular edema (spongiosis). Some of them present vacuolation of the nuclei and karyolysis. Mononucleares containing numerous irregular black stained granules in their cytoplasm (Mallory-Medlar-Lipschütz' cells) are sometimes noticed associated to such epidermal changes.

Corium entirely normal.

Case 3334: — C. de A. S., a white female infant, six months old, was admitted to the Hospital São Francisco de Assis on October 27, 1931, presenting the clinical picture of measles.

Histologic examination (12 hours after the onset of the typical macular rash): — The stained sections of the specimen measure 2 x 1 mm.

The lesions involve both epidermis and corium.

Very small vesicles are seen near the stratum granulosum, and their contents are represented by desquamated and necrotic epidermal cells and a few polymorphonucleares (Fig. 1). Parakeratosis is found associated sometimes but not always to the formation of vesicles. A few polymorphonucleares infiltrate the stratum spinosum. A remarkable finding is the presence of multinucleate epithelial giant cells in the superficial layers of stratum spinosum (Fig. 3). This is reminiscent of changes described in chicken pox (illustrated by Kyrlé, 1927, Bd. II, S. 46, Abb. 23).

Perivascular infiltration of the superficial blood vessels by mononucleares with occasional presence of Mallory-Medlar-Lipschütz' cells (Fig. 2) is also found.
Case 3 362: — W.F., a colored boy, 5 years old, was admitted to the Hospital São Francisco de Assis presenting the clinical picture of measles, the macular rash starting in the head and trunk. A biopsy of the skin was performed in the lumbar region, the last one which was affected at the time.

The subsequent course of the disease was normal.

Histologic examination (about 14 hours after the onset of the eruption): — The changes in the epidermis are slight and represented by hyaline necrosis of solitary epidermal cells. Sometimes two or three adjoining cells are affected by preference in the superficial layers of the rete malpighi. Rarely the necrotic cells are situated in the basal layer.

There is slight infiltration around the superficial plexus of blood vessels by mononuclears with occasional presence of Mallory-Medlar-Lipschütz' cells as well as necrosis of fusiform cells in the adventitia. As a consequence of karyorrhesis of such elements irregular extracellular chromophilous granules are produced.

Case 3 539: — M. de M.C., a white boy, 2 years old, was admitted to the Hospital São Francisco de Assis showing the early symptoms of measles: fever (39°C.), reddening of the conjunctivae, coryza and Koplik’s spots.

A biopsy of skin was performed in the scapular region.

Histologic examination (14-16 hours after the onset of the eruption): — The stained sections of the specimen measure 3 x 2 mm.

In the upper layers of rete malpighi detached necrotic epidermal cells and a few polymorphonuclears are seen collected in small vesicles (Fig. 4). The nuclei of the necrotic prickle cells are vacuolated and shrunk.

Mallory & Medlar (1920, Plate XXVII, Fig. 13) describe apparently similar changes which they refer as “two small pustules” (pg. 348).

Parakeratosis is sometimes found near the vesicles and pustules as well as spongiosis and infiltration of the prickle layer by solitary polymorphonuclears.

Peculiar changes are found at times in the parakeratotic cells (Fig. 4 and 5). Many of them contain striped intranuclear acidophilic bodies which were once referred by Torres & Teixeira (1932, b) as “inclusions acidophiles en bande”.

Case 3 284: — M.P.S., a white female, 18 years old, resident in Correntes (northern part of Estado de Minas Gerais) was admitted to Hospital Oswaldo Cruz on May 17, 1931. She was found to present anemia, edema of the legs and fever in alternate days.

Malaria and ankylostomiasis was diagnosed. When convalescent she was exposed to the contact of a child admitted to the same hospital and which developed measles.
Actual disease (measles): — September 4, 1931: the anemia is much improved, the patient feels well and has no fever. Sept. 6: — slight vespertine rise of temperature. Sept. 8: — the patient develops coryza, sore throat, reddening of the conjunctivae and photophobia. Sept. 9: — she presents the same picture and Koplik’s spots are observed. Sept. 11: — the condition of the patient is somewhat improved, and the temperature is normal. Sept. 12: — the temperature rises to \(38^\circ.8\) C., the patient is uneasy and depressed; the macular rash starts in the head and thorax. Lungs show no dullness on percussions. Sept. 13: — the macular rash of a rather confluent nature typical of measles is well established. A small piece of skin was removed (at 10 h. a.m., approximately) from the dorsal region. Sept. 14: — the stage of desquamation takes place. Sept. 15: — the stage of desquamation takes place. Sept. 18: — the patient is entirely recovered.

Histologic examination (18 hours after the onset of the eruption, 4th-5th day of disease): — Minute vesico-pustules (Fig. 8) appear in the superficial layers of stratum spinosum, immediately beneath the stratum granulosum. Their contents are represented by desquamated and necrotic epidermal cells and a few polymorphonuclears, and occasionally pigment. Infiltiration of the rete malpighi by polymorphonuclears which are more numerous near the vesico-pustules (Fig. 8). Necrosis of epithelial cells singly in the middle and superficial layers of stratum spinosum. Identical changes are sometimes seen in Langerhan’s cells. Mitotic figures are often found in the basal row and the next ones.

Parakeratosis is almost always coincident with the vesicles and vesico-pustules. At times the parakeratotic cells show a condensation of the intranuclear material in an acidophilic strip attached to the nuclear membrane by its extremities (cells with TORRES-TEIXEIRA’s bodies, Fig. 7). The basichromatin is settled on the nuclear membrane and partially in the surface of the intranuclear body which is separated from the nuclear membrane by a clear zone.

Fig. 6 represents older lesions in which the pustules have dried up forming thickened plaques in and beneath the cornified layer.

Marked infiltration (by macrophages and polymorphonuclears) do exist in some papillae while others look normal.

The superficial blood vessels present marked perivascular infiltration (Fig. 6) with predominance of macrophages while polymorphonuclears and eosinophils are less numerous. Pale brownish granules of pigment reminiscent of melanin as well as polymorphonuclears are englobed by the macrophages. The great number of such pigmented cells is impressive in some fields examined. MALLORY-MEDLAR-LIPSCHÜTZ’ cells are not numerous in the exudate and their granules smaller, more irregular and not so abundant as those found in the melanin-containing macrophages. A few of them infiltrate the stratum spinosum.

Case 3 514: — C.P.L., a colored boy, 3 years old, was admitted to the Hospital São Francisco de Assis on August 26, 1932 presenting
the clinical picture of measles. Opinions were divided as regards the begining of the eruption, the parents stating that it started two days before while the physician had the impression of a measles rash of approximately twenty hours duration. The patient had a recent history of pleuritis.

A biopsy of the skin was performed in the scapular region.

Histologic examination (20 hours (?)) after the onset of the eruption: — The stained sections of the specimen measure 3 x 2 mm.

The changes are more marked in the papillae which show infiltration by polymorphonuclears and a few macrophages. The infiltration of the basal row by a small number of polymorphonuclears is associated to singly hyaline necrosis of the neighboring epidermal cells.

Spongiosis is found in the superficial layer of the stratum spinosum exactly in the place occupied by the vesicles and pustules seen in other patients. The spongiosis is focal in character and associated to slight infiltration by polymorphonuclears, and the impression is gathered that they probably correspond to early lesions preceding the formation of vesicles and pustules.

Perivascular infiltration (by macrophages and a few polymorphonuclears) is seen in the corium. Free granules of brown pigment similar to those existent in the basal layer appear in the exudate.

Case 3 394: — S.E., a white, girl, 5 years old, was admitted to the Hospital São Francisco de Assis on March 21, 1932, presenting the clinical picture of measles.

A biopsy of the skin was performed in the lumbar region where the eruption was well developed.

Histologic examination (about 20 hours after the onset the eruption): — The stained slides measure 6 x 1 mm.

There is hyaline necrosis of epithelial cells singly and in clumps with spongiosis, infiltration by a few polymorphonuclears, and formation of minute vesicles.

Parakeratosis is sometimes associated to the above mentioned epidermal changes. Peculiar cells presenting nuclear changes formerly described by Torres & Teixeira (1932 b) as “inclusions intranucléaires en bande” are found in some of the parakeratotic areas.

Edema of the papillae and moderate infiltration by macrophages around the superficial vessels, and a few Mallory-Medlar-Lipschütz’ cells are seen.

Case 3 558: — E.R., a colored female infant, 18 months old, was admitted to the Hospital São Francisco de Assis on October 17, 1932, presenting the clinical picture of measles. The macular rash was still generalized, and a biopsy of the skin was performed in the scapular region.
Histologic examination (about 20 hours after the onset of the eruption): — The changes are very slight in the epidermis, and were evidenced but in two fields. In one of them there is spongiosis, hyaline necrosis of epidermal cells, and infiltration by macrophages. In the other, a minute pustule is found.

The perivascular infiltration in the corium with predominance of macrophages is present, and possibly more marked than usual. MALLORY-MEDLAR-LIPSCHÜTZ cells are scanty.

Case 3 323: — M.L.M., a white girl, 10 years old, was admitted to the Hospital São Francisco de Assis on October, 10, 1931.

The patient is a typical case of measles in the fifth day of disease; the eruption had the approximate duration of twelve hours on admission.

Histologic examination (about 36 hours after the onset of the eruption): — Hyaline necrotic epidermal cells, generally single (Fig. 9) are seen in the middle and superficial layers of stratum spinosum. Fig. 10 shows a thickened plaque consequent to pustule which begins to dry up. Polymorphonuclears do not have a large part in the formation of the crust as is the case in small-pox and alastrim's pustules.

Perivascular infiltration by large mononuclears, lymphocytes, rare polymorphonuclears and MALLORY-MEDLAR-LIPSCHÜTZ' cells are seen in the corium.

Very recent changes such as the hyaline necrosis of single epidermal cells are very conspicuous and associated to advanced changes (pustulation and crust-formation).

Case 3 510: — D.M.S., a colored female, 19 years old, was admitted to the Hospital São Francisco de Assis on August 22, 1932.

The patient is a case of measles presenting a typical generalised rash.

A biopsy of the skin was performed in the right external femoral region, four transverse fingers above the knee joint.

Histologic examination (about 72 hours after the onset of the eruption): — The epidermis is normal.

Pathological changes are found only in the corium, and are definitely less marked than usual.

Large mononuclears and a few MALLORY-MEDLAR-LIPSCHÜTZ' cells form well-defined mantles of cells about the vessels, and a moderate proliferation of fibrocytes is noticed.

DISCUSSION

The histology of the skin lesions in measles is little known, and misleading information is to be found even in such excellent text-books such as SMITH & GAULT'S "Essentials of Pathology".
Referring to the Koplik spot they state that the histologic studies suggest an allergic type of reaction, although it may well be the direct reaction to the presence of virus locally. "It consists of acute hyperemia with perivascular cellular infiltration in which particularly large mononuclear cells predominate. The skin rash is similar in its histologic appearance" (pg. 184).

This is in complete disagreement with real facts: the minute vesicles and pustules early described by Ewing (1909) and by Mallory & Medlar (1920) are completely ignored, which is certainly a great handicap in the appreciation of the pathogeny of the skin lesions.

In a great number of erythemas it is not easy to decide the sequence of the appearance of the changes in the epidermis and in the cutis (s. Kyrle, 1927).

Rather extensive cellular infiltration may appear in the cutis while the epidermis still remains normal, in erythema toxicum (s. Kyrle, 1927, Ed. II, Abb. 5), and the same is true in erythema papulosum (s. Kyrle, loc. cit., Abb. 6).

This question is not settled as regards meases.

Epidermal lesions are mentioned by Catrin (1891), Ewing (1909), Mallory & Medlar (1920), and Abramow (1921).

Catrin's work is based on the study of autopsy material from a patient dead of "rougeole boutonneuse" four days after presenting "du catarrhe oculo-nasal, etc.", and it seems likely that besides the changes peculiar to measles he dealt with others produced by secondary infections. This would be an explanation for the lesion which de identifies to "phylactènes profondes".

Some of the assertions found in Ewing's paper were inaccurate, and this explains the general disrepute in which it fell later on. However, Ewing correctly describe some of the more important changes as focal necrosis of epidermal cells, and formation of minute vesicles.

Mallory & Medlar have considered the cell changes in the epidermis as probably secondary to the inflammatory process in the corium.

Quite different is the assertion of Abramow which says textually: "... so müssen wir annehmen dass es bei Masernhautveränderungen zu einer primären Epithelaffektion kommt:..."

Kyrle (1927) considers measles and scarlet fever erythema as instances of simple inflammatory reaction. Pertaining to the group of scale forming erythemas, they were expected theoretically to present primary epidermal changes while in the other group ("nichtschuppende Erythema") scale formation and epidermal changes never occur.

Nevertheless Kyrle (loc. cit., S. 28) illustrating measles exanthema describes moderate inflammation in pars papillaris while the epipermis appears microscopically normal. Considering the scarlet fever erythema he maintains the view that epidermal lesions may escape notice when the usual histologic methods are employed, while colloidal chemical changes influencing normal cornification are at work.
Epidermal and dermal changes are described in this paper.

Interesting similarity not generally recognized are reported here between the epidermal changes in measles and other virus diseases presenting dermatotropism. Minute vesicles and pustules occur, and this is confirmative of previous work (Ewing, 1909, Mallory & Medlar, 1920).

Parakeratosis is often found, and in some cases the parakeratotic cells develop peculiar changes in their nuclei: there is condensation of all the intranuclear material in a strip deeply stained by the eosin attached to the nuclear membrane by theirs extremities. The intranuclear body is separated from the nuclear membrane by a clear zone or “halo”. The basichromatin is condensed on the nuclear membrane and at less extent upon the intranuclear body.

Those changes were first described by Torres & Teixeira (1932 b) as “inclusions intranucléaires “en bande”, and could not be found in slides of normal skin (in regions with a well developed stratum granulosum) eczema, psoriasis, lupus and cutaneous leishmaniasis studied by comparison.

It is recognised that the inclusion bodies in large viruses are simply intracellular clusters or colonies of elementary bodies, and as Pinkerton (1950) remarks, intracellular clusters formed by bartonellae and rickettsiae differ in no essential way from certain of the cytoplasmic viral inclusions.

In psittacosis and lymphogranuloma venereum the organisms or elementary bodies are embedded in a matrix, and it is not clear whether this matrix is contributed by the organism or by the host. In vaccinia and ectromelia viruses the cytoplasmic inclusions have a matrix composed of lipoid material usually surrounded by a capsule-like membrane (Himmelweit, 1938), and contain elementary bodies.

In smaller viruses the inclusions are homogeneous and supposed to be formed by exceedingly minute elementary bodies and their secretions, with or without the addition of a matrix formed from cytologic constituents (Pinkerton, loc. cit.).

Recent work of Wyckoff & Smith with the aid of electron microscopy has shown that the polyhedral bodies which develop in the nucleus in such large numbers in virus infections of insects are crystalline inclusions with virus particles readily discernible on the surface. In some cases a membrane is found surrounding the polyhedral bodies, and a marked irregularity occurs near the center of the body.

In conclusion, a matrix formed from cytologic constituents (in other words, peculiar retrograde changes) and secretions of the minute elementary bodies themselves are therefore recognised by most authorities as forming many of the inclusion bodies besides the elementary bodies.

The intranuclear bodies of Torres-Teixeira found in measles somewhat resemble the intranuclear changes described in the nuclei of epidermal cells in small-pox and alastrim (Torres & Teixeira, 1935, a,
b, Torres, 1936), and correspond in part at least to specific retrograde changes. If they are or are not associated to elementary bodies is another question not yet settled here as well as in several intranuclear bodies of virus diseases.

In the meantime it seems more reasonable to consider all those specific nuclear and cytoplasmic changes as "viral inclusions", the real importance of them being their strict specificity, and accept the view that they represent, in part at least retrograde changes of a peculiar kind.

In our material it was clear that the primary changes were localized in the epidermis (in case 3364, for instance, where the biopsy was made 10 hours after the onset of the eruption), and this confirms the idea of a direct injury of the epidermal cell by the virus.

Kyrle (1927, S. 22) says that: "... ein Toxin, das mit der Blutwelle in den Papillarkörper kommt und dort abgesetzt wird, muss zwangsläufig auch in die Epithelymphre übergehen und an die MALPIGHIT schen Zellen herankommen..."

In which way epidermal changes could produce inflammation?


However it is often impossible to decide which tissue, epidermis or corium is the seat of the initial injury.

The circumstance that changes of the same kind are found both in epidermis and corium in the eruption of several cases of measles examined microscopically is well demonstrated in this paper. In other words, the measles eruption presents an uniform histologic picture.

In this respect a proper consideration should be given to unavoidable sources of error, the impossibility to determine accurately the time of onset of the eruption being of course the first to be remembered.

If the biopsy of skin is performed when physical examination had established a probable duration of 14 hours, for example, for the rash, it is possible and even probable that besides the changes belonging to this stage, more recent and quite recent ones could be included in the skin fragment obtained, and this will explain the finding of several stages in the same specimen.

In case 3362, for instance, the biopsy was performed approximately 14 hours after onset of the eruption and the changes correspond evidently to a stage less advanced than those found in case 3364 in which the duration of the rash was estimated in 10 hours. A disparity between the duration of the eruption and the actual stage of the lesions was remarked also in case 3362 and 3539. In case 3323 the biopsy was performed 36 hours after the onset of the eruption and later stages with pustulation and crust formation were found side by side with very recent changes such as the hyaline necrosis of single epithelial cells.
In the exudate of the skin lesion in measles are found large mononuclears containing in their cytoplasm numerous irregular deeply stained granules (Fig. 2) which were formerly considered an outstanding detail in measles lesions. Such granules were regarded by Lippschütz (1929 a and b) as representing "Erkrankung des Mikrozentrums". They have been first recorded by Mallory & Medlar (1920) who were unable to decide the true nature of them (digested remains of phagocyted leucocytes or lymphocytes?, retrograde changes within the cells?, enlarged centrosomes?, parasites like the infectious agents in Oroya and coast fevers?).

Our observations suggest a possible relation of such granules to keratohyaline granules. They give a positive Feulgen's reaction (Torres & Teixeira, 1932 c) and contain therefore thymonucleinic acid. This does not favour the view of a relation between such granules and pathological centrosomes. A nuclear origin for them have been suggested by Torres & Teixeira.

While the question of the origin of the keratohyaline granules is not settled yet, some authors think that: "... die Körnchen seien nichts anderes als abgesplitterte Kernsubstanz allerdings in bestimmter Weise verändert..." (Rabl, cit. by Kyrle, 1925). This and the not uncommon presence of Mallory-Medlar-Lippschütz, cells in stratum spinosum suggest that they are macrophages with phagocyted keratohyaline granules. We have seen that parakeratosis is a regular finding in the skin lesions of measles and the tropism exerted by the virus on macrophages is a well established fact.

Active multiplication of epidermal cells and consequent formation of multinucleate giant cells (Fig. 3) in the superficial layers of stratum spinosum (the usual site of vesicle and pustule formation in measles) could be demonstrated in case 334. This is somewhat reminiscent of the so-called Warthin-Finkeldey giant-cells so often recorded in prodromal stages of measles. Curious enough was the coincidence of their occurrence in one of the earliest skin biopsy obtained (12 hours after the onset of the eruption).

Cell hyperplasia is often the result of direct action exerted by the virus on the tissues. An advantage of this was taken, for instance, in the diagnosis of chicken-pox: the finding of giant-cells in smears from the early skin lesions is considered as a strong support for a positive diagnosis.

It looks as if in measles such cell hyperplasia determined by the virus is less marked than in alastrim (Torres, 1936), and considerably less than in chicken-pox. They represent, however, similar changes, and have in this account a speculative interest.

Hyaline necrosis of epidermal cells single or in small clumps represent an early change which was regular in almost all the stages of the eruption studied. Fig. 9 represents a typical scattered necrosis found 36 hours after the onset of the eruption and similar changes were met in cases 3362, 3284, 3394 and 3558 examined respectively 14, 18, 20 and 20 hours after the onset of the exanthema.
This leads to the view that the virus is able to renew the deleterious action exerted upon the epidermal cells over a considerable period of time, and gives rise to quite recent changes even 36 hours after the onset of the eruption when older lesions are still healed in part or completely.

CONCLUSIONS

Epidermal changes are a regular finding and show a typical microscopic picture in measles eruption.

Clumps of swollen epidermal cells in the superficial layers of stratum spinosum represent apparently the initial change being associated to spongiosis and the occasional presence of MALLORY-MEDLAR-LIPSCHÜTZ' cells (large mononuclears containing deeply stained irregular granules).

The corium was normal in the piece of skin examined 10 hours after the onset of the eruption while epidermal lesions were still present, sometimes limited to a few cells near the stratum granulosum.

Very soon, however, dermal changes are found, and in fact all specimens examined since 12 hours after the onset of the eruption show both epidermal and dermal lesions.

Besides the hyaline necrosis of epidermal and Langerhans cells single or in clumps, formation of vesicles is found twelve, fourteen and sixteen hours after the onset of the eruption. The minute vesicles are seen near the stratum granulosum, and contain very small amount of fluid. Most of their content is represented by desquamated and necrotic epidermal cells, and a few polymorphonuclears; pigment (melanin?) is also occasionally found.

Parakeratosis is seen near the vesicles, and some of the parakeratotic cells contain striped intranuclear acidophilic bodies (TORRES-TEIXEIRA's bodies). The basichromatin is deposited upon the nuclear membrane and in part on the surface of the intranuclear body (Figs. 4, 5 and 7), a clear zone separating such structures. The cells with TORRES-TEIXEIRA's bodies probably correspond in part to specific retrograde changes within the cells as is the case with similar nuclear changes in epidermal cells described in small-pox and alastrim (s. TORRES & TEIXEIRA, 1935 a and b). In such diseases they were formerly considered as intranuclear bodies.

In the papillary layer there is edema and infiltration by large mononuclears, a few polymorphonuclears and eosinophils, and occasionally macrophages containing brown pigment (melanin?).

Perivascular infiltration by large mononuclears is seen in the reticular layer. The changes found in the corium are not described here in detail as they are well known and referred by almost every previous author.

Large mononuclears containing irregular deeply stained granules in their cytoplasm (MALLORY-MEDLAR-LIPSCHÜTZ' cells) are found in va-
riable amount in the epidermis or in the corium. Data were obtained which suggest the possibility of such cells representing macrophages with kerotohyaline granules phagocited, a probable result of changes in the process of cornification induced by the virus.

Epidermal giant cell formation is present in early stages (12 hours after the onset of the eruption).

No epidermal changes could be demonstrated 72 hours after the onset of the eruption while well defined mantles of cells (large mononuclears and Mallory-Medlar-Lipschütz' cells) were found about the vessels in the corium associated to moderate proliferation of fibrocytes.

Very recent epidermal lesions (hyaline necrosis of epithelial cells singly or in clumps) could be demonstrated in every biopsy examined between 10 and 36 hours being associated to other changes in different stages of development.

This suggests a lasting noxious action exerted on the epidermal cells by the virus.

Vesicle and pustule formation previously referred in measles eruption by several authors (Ewing, 1909, Mallory & Medlar, 1920) is wholly confirmed, and this is very clear when the pieces of skin are submitted to microscopic examination.

Apparently this important histologic detail did not receive due attention in the literature.

Measles is usually considered in the group of exanthematic virus diseases together with rubella, fourth, fifth and sixth diseases and sweating sickness (S. Gildemeister, Haagen & Waldmann, 1939). The microscopic study of the eruption, however, discloses similitudes with the lesions found in the group of pustulous virus diseases (chicken-pox, zoster, small-pox and alastrim).

**SUMMARY**

Hyaline necrosis of epidermal cells either single or in clumps represents apparently the primary change in the measles eruption.

Lesions occur, however, very soon in the corium and could be demonstrated twelve hours after the onset of the eruption.

The early lesions (twelve to thirty-six hours) in the epidermis show usually different stages in a single slide examined. They are described as minute vesicles and pustules; in older lesions the pustules have dried up forming thickened plaques in and beneath cornified layer.

Parakeratotic cells with intranuclear bodies first described by Torres & Teixeira (1932 b) while inconstant are regarded as a pathognomonic change in measles eruption.

Edema of the papillary layer and perivascular infiltrations in the reticular layer by large mononuclears some of them containing small irregular deeply stained granules (Mallory-Medlar-Lipschütz' cells)
are well known changes largely referred in the literature. Evidence is here submitted in support of the opinion that such cells correspond to macrophages with keratohyaline granules phagocited as a consequence of changes in cornification determined by the virus itself.

Microscopic examination is necessary for the demonstration of the minute vesicles and pustules which are such an important detail in the histology of the measles eruption as it establishes connections between measles usually considered in the group of exanthematous diseases with chicken-pox, zoster, small-pox and alastrim (pustulous diseases).

Epidermal changes are no more found seventy-two hours after the onset of the eruption while well-defined mantles of cells about the vessels and a moderate proliferation of fibrocytes is noticed in the corium.