Numerous works deal with the cause of skin diseases caused by a filterable virus. Recognized among these in this field are the works of Lipschütz, also the communications of Kummer and Nicolau at the Budapest conference, further the investigations of Ravaut and Ferrand and finally those of P. Blum on viral diseases. In these works it emerges that some authors, for example Kummer, associate aphthae with herpes. Others though regard herpes as one of the neuro-dermatrophic infections. Some researchers have succeeded in confirming the viral etiology of certain aphthous manifestations, while others have not arrived at any final conclusions.

The cases which are to be discussed below demonstrated the following clinical picture: lesions of the mouth, the genitalia and the eye. These lesions however are not the same as the aphthoids of Popischil, and the as yet little researched skin lesions which one often encounters in children.

When one individually examines the lesions which appear with recurrences with respect to their localization, it becomes evident that the oral and genital syndromes can be divided into two groups. So for example the aphthous ulcers in our second case occasionally first occur on the genitalia and are initially reminiscent of Lipschütz ulcers or various forms of mucosal ulcerations (Esthiomène). With the relapses which occur several times a year, however, the lesions appear either simultaneously or...
sequentially in the mouth, the genitalia, the conjunctivae, and even as inflammation of the iris. These manifestations deserve to be examined separately.

In one of the patients whom we have been following for 20 years, very painful lesions reminiscent of erythema nodosum appeared in the first years at the time of the relapse. As soon as the aphthous lesions of the mouth and genitalia were resolving, the skin lesions were also disappearing. In both our cases, who have had periodic relapses for 20 and for 7 years respectively, one cannot regard the aphthous manifestations as common aphthosis. It is also of note that the respective relapses of the aphthous lesions of the mouth or the genitalia (on the penis or the scrotum of men; on the vulva or the vagina of women) are accompanied by inflammation of the conjunctiva. This fact as well as the observation that local treatment is ineffective, but that it was possible with systemic treatment, to increase the intervals between the relapses, suggest that this is a disease caused by a generalized infection which affects the entire body, and that the aphthous lesions have nothing to do with common aphthosis. We did not fail to consider any probability or even only possibility in investigating the aphthous syndrome. So for instance we considered the Hugier syndrome in light of the edematous hypertrophic vaginal syndrome of our second patient. Also considered were tuberculosis, the Nicolas-Favre symptom complex, syphilis, diphtheria, simple chronic vaginal ulcers, the venereal ulcerations of Walander, Mac Lead-Donovan disease, granuloma nostras of Gougerot-Blum, dermatitis herpetiformis of Duhring, hydroa bulbosa superficialis, and diabetic efflorescences of the genitalia. The aphthous lesions of the mouth occurring with the relapses (in both patients) do not entirely correspond to typical oral aphthae. Other differential diagnostic considerations included: erythema exsudativum, pemphigus, various kinds of mucosal ulcerations, even the relapsing chronic skin lesions of Mikulicz, although these are different in type and development. For a time we also considered neurotic ulceration of the mucous membrane (Löblowitz). Because of the periodic relapses, the involvement of only the oral mucosal membrane and the divergent clinical picture, all of these suppositions were rejected. The fact that the eye was involved made us doubt the possibility, for example, of a neurotic ulceration.

The negative result of all of our investigations and the periodic, sometimes simultaneous, sometimes sequential appearance of the lesions in the mouth, vagina, scrotum and the eyes gradually lead us to the conviction that this must be a viral disease which affects the entire body. My histologic examinations did not result in the elucidation of either of the two cases. The sections demonstrated only a chronic inflammation with round cells and a thickening of the vessel walls in the deep tissue. The serial sections, which were treated with a variety of staining methods, were also without result. A search for tuberculosis, and animal inoculations were negative as well. The occurrence of a new eruption of the mouth, scrotum and eye in the form of a traumatic ulceration of the cornea, perikeratitis and serous iritis, lead our first patient to turn to the Viennese professors Fuchs, Sachs, Finger and Kyrle (1919-1920). Since this attempt was not successful either, the patient returned to Istanbul (1920). In Vienna, as in Istanbul, some physicians attributed the manifestations to tuberculosis, while others assumed a particular parasite was responsible. Consequently the patient was treated with gold and trivalent arsenic. Thanks to this therapy the relapses which until then had occurred 4 to 5 times a year became less frequent and the pains diminished. However, a short time later the usual relapses recur. During the respective attacks with aphthous injury to the mouth and scrotum, the Istanbul ophthalmologists initially diagnosed a kind of traumatic ulceration of the cornea. During later relapses the congestive perikeratitis resulted in an insignificant purulent accumulation in the anterior eye chamber and finally in a serious iritis with occasional bleeding of the conjunctivum (Figs. 1-4).

According to information from Professor Niyazi Gözeie iridectomies were

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**Fig. 1.** Aphthous ulcers of the genitalia of pt. L.D.

**Fig. 2.** Relapses occurring at different times in the same patient.

**Fig. 3.** Aphthous manifestations in the mouth and on the lips.

**Fig. 4.** Relapses in the mouth, lesions resembling Perleche.
HISTORICAL VIEW

performed in Vienna. Currently the left eye is almost completely blind due to atrophy of the eyeball, while the right eye can scarcely detect light.

Our first case is a 40-year-old man, healthy, without physical deformity, married and father of healthy children.

Our second case is a 34-year-old, physically entirely normal woman and mother of healthy children. The disease began some 7 years ago in this woman (L.D.) with lesions on the tongue, which spread to the tonsils, uvula and the lips and after some time affected the genitalia. The lesions of the mouth, especially those of the lips, resembled the so-called “angulus infectious oris” (Perlèche) and interfered with the patient’s eating and drinking. As a result of this the patient had marked weight loss with every relapse. The aphthous, edematous lesions of the genitalia were also very painful and in places had the appearance of purpura-like ecchymoses. The particularly severe recurrences also caused corneal erosions and episcleritis (Igersheimer-Murat Rami). The eruptions each lasted 20 to 30 days, the manifestations then slowly subsided, her appetite returned, so that the patient made up for the weight loss and returned to her baseline weight (Fig. 5).

The histologic examination of the oral and genital lesions, the Frei reaction, culture according to Löwenstein, animal experiments as well as the search for diphtheria bacteria produced only negative results. The general examination of both patients also produced no abnormal findings: neither the roentgenogram of the lungs nor the skeletal examination, the qualitative and quantitative hematologic examination nor the most extensive metabolic tests produced an abnormal result (Figs. 6, 7).

Last year, in the face of the clinical picture described here, we initiated a collaboration with Professor Braun, head of the Institute for Microbiology of the University of Istanbul. Professor Braun
undertook microbiologic examination of smears of the oral and genital lesions on multiple occasions with each relapse. In the smears of our second patient stained according to Giemsa and Herzberg he found a structures resembling elementary particles of a virus, which were seen in the smears of our first case in even greater numbers. Professor Braun also examined smears of three further patients from my clinic as controls, who had common aphthosis of the mouth or the genitals. However, he did not find any structures elementary particles resembling elementary particles of a virus in these. Further investigations will be pursued from this point of view when cases of aphthous manifestations appear.

Below the summary of our report made together with Prof. Braun to the Dermatological Society of Istanbul (meeting of May 11, 1937).

Microscopic findings from the ulcer base from Mrs. L.D.:
Gram stain: abundant leukocytes and epithelial cells, intermingled with rods and cocci.

The cultures revealed that the microorganisms were saprophytes.
Giemsa stain: Leukocytes, epithelial cells, bacteria as well as very abundant, extraordinarily small, red-violet stained, roundish particles, in part extra-, in part intracellularly located. The size of these particles is about that of the smallpox virus (Figs. 8, 9).

It should be noted that we took the samples from the patients at three different time points and each time the findings were the same (see Fig. 6). Because of the similarity of the structures to the elementary bodies of a virus, staining with Victoria blue according to Herzberg was carried out. With this stain too, structures suspiciously resembling a virus were demonstrated (see Fig. 7). In order to counter the objection that these were perhaps artifacts, the following tests were conducted.
The air-dried smears were treated with ether alcohol to extract possible lipoids. After subsequent treatment with Giemsa and Herzberg stain enormous numbers of virus like structures were found.

Further we pretreated the air-dried smears with 3% acetic acid for ¼ hour in order to eliminate possible precipitates, and then stained them. Nonetheless, the impression remained unchanged: there were abundant structures resembling elementary bodies.
If the specimens are pretreated with 3% soda-lye for ¼ hour, the viral structures no longer can be identified. The structure of the leukocytes and epithelial cells is then completely destroyed.

In accordance with these findings, the assumption is at hand that the present infection is caused by a virus. Naturally this conclusion can only be drawn when the same findings are demonstrated in many patients of this kind. It must be considered that there are saprophytic viruses, which could proliferate in ulcers exactly like saprophytic bacteria. It will therefore be necessary to use ulcers of known etiology (carcinoma, lues, tuberculosis etc.) as controls for all stains.

We also transferred the virus to scarified rabbit cornea, but as is evident from the report of Professor Igersheimer, no local or generalized infection can be produced. It will be necessary to employ other types of infections and other animals in subsequent investigations.

Abundant structures resembling elementary bodies were also demonstrated in the specimens from the ulcer base of patient H. stained according to Giemsa as well as Herzberg. These resemble in their staining, size and arrangement, those which we had seen in the woman with genital ulcerations.

In contrast, we were unable to demonstrate with certainty any structures which could be regarded as elementary bodies in any specimen of the smears which were taken from the aphthous oral lesions of patient Z. and patient J.
The two patients still continue to be followed. During the last relapse we performed a biopsy of the aphthous, hypertrophic, edematous ulcers on the vulvae of our second case. Only rudimentary changes of chronic inflammation were seen, which we ourselves had also previously observed. Distinctive cellular inclusions are absent. See Figs. 8 and 9 for the histology report of Prof. Obundorfer.

In a second communication I will report on the findings of further investigations as well as animal experiments addressing the viral etiology of the disease manifestations described here.