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CHAPTER IV

QUESTIONS OF PATHOGENESIS AND PATHOLOGO-ANATOMICAL CHANGES IN FOOT-AND-MOUTH DISEASE

THE PATHOGENESIS OF FOOT-AND-MOUTH DISEASE

The pathogenesis and pathological anatomy of foot-and-mouth disease has been given inadequate development by science, and many questions in this connection have not yet received exhaustive scientific elaboration. Completely inadequate is our information with respect to the full picture of pathologo-anatomical and histological changes in the organs and tissues of animals which have died from foot-and-mouth disease.

At the present time science has cast considerable light on questions of the means and methods of infection, and also of the epizootological significance of various secretions of the organism of the sick animal. Under conditions of natural development of an epizootic, as already stated, animals are infected by means of direct contact of a sick animal with a healthy one, or through transmitters of various types. In the latter case the virus can make its way to the organism of healthy animals with the secretions and excretions of sick ones, together with fodder, drinking water, litter, objects used in husbandry, et al. Infection is also possible through infected milk fed to calves and pigs. From literature on the subject cases of intrauterine infection are known. It is assumed that there is also a possibility of infection through the sexual organs. Basic channels of penetration of the virus into the organism of the

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susceptible animal are the digestive tract, the respiratory apparatus, the udder, and the extremities. With respect, then, to the mechanism itself of the development of infection in the organism individual investigators of this question have various views.

Loeffler and Frosch expressed the hypothesis that the infective basis of foot-and-mouth disease penetrates into the organism of the animal through the digestive tract together with fodder or water, or is injected through abrasions in the region of exposed mucous membranes and skin, then gets into the blood, multiplies there (in the incubation period), and together with the blood is disseminated through the entire organism, causing at definite places the appearance of vesicular exanthema. Loeffler and Frosch did not consider contact of the virus with blood an essential condition for the development of infection in the organism. The blood was regarded by them as a culture medium for the virus; at the same time it is also a medium for the transportation of the virus through the organism. Incidentally, Nicolau and Galloway also assume that the virus can multiply in blood.

Most convincing is the hypothesis of Waldmann and Pape, who on the basis of their experimental investigations conceive the development of the foot-and-mouth-disease process in the following fashion.

The virus, received by the animal through the digestive tract or surface areas, penetrates into one of the defects in the epithelium, where it at first stays and multiplies. At this place, as a result of such "fixation" and multiplication of the virus a primary manifestation, or primary aphtha, develops. This incipient stage, which runs its course imperceptibly and habitually without visible clinical

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phenomena, was called the first phase of development of the foot-and-mouth-disease process by Waldmann and Trautwein. With the development of the primary aphtha on the site of penetration of the virus the latter, in the process of rupturing of the aphtha, penetrates the blood and together with the blood is disseminated about the entire organism. As a result of this generalization of the virus, at so-called "favorite points" (the buccal cavity, in the region of the interdigital space and coronary band of the extremities and the teats of the udder) secondary-plural aphthae develop. This stage of development was called by Waldmann and Pape the second phase of development of the foot-and-mouth-disease process. Entrance of the virus into the blood is always accompanied by a sharp increase in temperature and a subsequent development of the whole symptom-complex of the disease. With the development and appearance of secondary aphthae the virus disappears from the blood, and the temperature falls again to normal.

Consequently, the foot-and-mouth-disease process, according to Waldmann and Pape, develops in the form of two phases, and contact of the virus with the blood is not essential to its multiplication. As proof of the correctness of their hypothesis they cited the following experimental data: if the virus is injected intravenously, then it quickly disappears from the blood and is absorbed at its "favorite points", where it actually multiplies (primary aphthae); thence it again penetrates the blood and together with it is borne about the entire organism, in consequence of which secondary, plural aphthae develop at the "favorite points".

The process runs a completely different course in infection of cattle susceptible to foot-and-mouth disease by means of placing the

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virus on the surface of the membrane of the buccal cavity, which has been scarified in preliminary. In this case there takes place at the point of scarification, where the virus has been placed, the development of a primary aphtha (in the first 24 - 36 hours from the moment of infection), following which comes generalization of the infection and formation of secondary aphthae. All this permits Waldmann and Pape to express the assumption that the virus does not multiply in blood, but only that together with blood it is transported about the organism.

The appearance of the foot-and-mouth-disease process in the saliva of sick animals before the appearance of clinical symptoms of disease is explained by Waldmann and Nagel by a rapidly advancing generalization of the infection. With this they also explain the giving off of the virus from the organism of the animal with all secretions and excretions at individual stages of development of the disease.

In certain contradiction with these established explanations are the data of Soviet investigators (Ratner, Kudryavtsev, Leonov, and Molchanov). Using the physiological method, these authors tried to obtain virus-containing saliva from a sick animal by means of laying a fistula on the excretory canal of the parotid gland. However, the secretion of the animal's gland, which had in preliminary been infected with foot-and-mouth disease, contrary to the anticipated results proved sterile at all stages of development of the infectious process.

The authors consider that "the infectiousness of saliva of animals which have developed foot-and-mouth disease is the result of

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mechanical contamination of the saliva by virulent particles of mucous membrane, and this infectiousness is not a specific biological property of the saliva".

The actual mechanics of the penetration of the virus from the primary aphtha into the blood so far remains the subject of little investigation. From the fact that the time of generalization of the virus usually coincides with rupture of the primary aphtha, certain investigators (Houduroy and others) draw a conclusion as to a connection existing between this phenomenon and penetration of the virus into the blood.

Pielang affirms that the presence of the virus in blood can be proved only in the period of generalization of the infection. With the development of only one local process in the form of a primary aphtha the presence of virus in the blood cannot be proved. Gins and Fortner, on the other hand, have proved the presence of the virus in blood even without generalization of the infection, with the presence of only a few local irritations. Italian investigators have proved that the virus appears in blood as early as the prodromal period, with the appearance of barely perceptible hyperemia at the point of its entry, and remains until the end of the fever period.

With intravenous infection the virus, as a rule, disappears very rapidly from the blood, its concentration in the aphthae always being higher than the concentration in the blood. According to the data of the English Commission on Foot-and-Mouth Disease, virus taken from the contents of guinea-pig aphthae can infect experimental guinea pigs in dilution of 1:100,000, while when taken

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from the blood of these same animals during the period of high temperature it can cause infection only in dilution of 1:1000.

On the basis of Waldmann's and Pape's data and those of other investigators, it is possible to affirm that the intravenous method of infection is actually of little reliability. The cutaneous and intracutaneous methods of infection, on the other hand, are the most effective. The high sensitivity of the skin to the virus in the experiments of Vallee and Carre, Skomorokhov, Waldmann and Pape, and other investigators has again found its verification.

Frenkel studied the virus-content in aphthae which he had caused artificially, establishing that with intravenous infection the virus appears earlier in artificial aphthae than in aphthae which have developed naturally. The amount of virus in aphthae which he had caused artificially was always less than in aphthae which had developed naturally. The formation of artificially caused aphthae, as it turned out, hampers the development of aphthae on "favorite places". With intravenous injection the virus disappears very rapidly from the blood, and at the same time disappears also from the aphthae. The concentration of virus in primary and secondary aphthae is always considerably higher than in the blood of the same animals having foot-and-mouth disease. With intravenous injection the blood is also characterized by a rather high virus-content, but its amount is always greater in the aphthae. It is extremely probable, in Frenkel's opinion, that the virus is carried to the aphthae in the bloodstream; however, it is possible that the virus multiplies in the aphthae themselves.

Foot-and-mouth disease runs its course in the form of a septic process. The virus, localizing in various organs and tissues of

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the sick animal, causes deep pathological changes, in consequence of which come serious functional disorders of the whole system.

The epithelial localization of the aphthous process, as most typical of this sickness, has been connected by many investigators with the epitheliotropic nature of the virus. At the present time it is considered, however, that in the foot-and-mouth-disease process mucous membranes of not only cutaneous, but also of glandular type, are irritated, in both cases there being observed the same process of serous inflammation. The virus in the system of the sick animal, particularly in the period of generalisation of the infection, has been proved not only at the "favorite points" (the membrane of the buccal cavity, places on the skin not covered with hair), but also in all parenchymatous organs, the muscles, the salivary and lymphatic glands, in bone and spinal marrow, in the brains, and other organs.

Pathological changes as the result of the action of the virus on the animal's system can be observed in the skeletal musculature, the parenchymatous organs, the lymphatic and salivary glands, the stomach-intestinal tract, and other organs. In addition there is an ever-increasing accumulation of data pointing to the participation in the foot-and-mouth-disease process of the central and peripheral nervous system.

Most typical of the foot-and-mouth-disease process is considered the formation of aphthae at "favorite points". These aphthae represent vesicular formations of various size, filled with yellowish, transparent or slightly clouded fluid -- serous exudate. (The serous exudate of aphthae is called "aphthous lymph", which from the scientific point of view is incorrect.)

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According to the data of Zschokke, Kallert, and also Ioest, primary changes occur, in the form of degenerative processes in the cells, in the middle layers of the epithelium, i.e. in the Stratum spinosum. The degenerative changes are characterized by swelling and thinning of individual cells and the transformation of the protoplasm of the latter into a homogeneous mass, by deformation of the nucleus of the cell, by coagulation of the chromatin, and vacuolization and reticulation of the protoplasm. In the final sum these degenerative changes in the Stratum spinosum end in colliquative necrosis. The inflammatory processes are accompanied by emigration of neutrophil leucocytes and simultaneous entry into the degenerated epithelium of serous exudate. As a result of the degenerative process and the thinning out of degenerated cells intraepithelial empty spaces are formed, which fill with serous exudate. The horny layer, i.e. the Stratum corneum, remains unharmed during this. In consequence of the accumulation of serous exudate in the epithelium, the overlying layers of the epithelium (Stratum corneum, Stratum lucidum, Stratum granulosum) and the upper layer (Stratum spinosum) are raised up, forming ultimately in the shape of a vesicle (aphtha).

As is evident from a description of the histogenesis of aphthae, the virus exercises its pathogenic effect first of all on the epithelial elements, the cases of pathological changes of the Submucosa observed in these irritations being duly regarded as phenomena of secondary order. The development of aphthae, independently of their place of localization and the type of animal, occurs usually in one and the same manner.

The question of the mechanics itself of the virus' effect on tissue remains unexplored. Certain investigators (Akulov, Gins, and others)

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assume that the virus is capable of developing toxins and with the help of the latter of manifesting its effect on tissue. This question, in our opinion, is somewhat debatable, since it is based only on the strong reaction on the part of individual systems and organs, particularly the vascular system, the liver, the suprarenals, the heart, and other organs, and also on sharply defined processes of degenerative fattening.

Bol' and Akulov, and also Ivanov and Akulov, have carried out very interesting investigations in connection with determination of the reticulo-endothelial system's part in the foot-and-mouth-disease process. Investigating pathological material, taken at various stages of the process, these authors observed a definite reaction on the part of elements of the reticulo-endothelial system in the liver, spleen, lungs, lymphatic glands, and other places. This question, as is known, remained unclarified for a long time, but it is now possible to speak definitely of the fact that the reticulo-endothelial system is also involved in the foot-and-mouth-disease process.

PATHOLOGO-ANATOMICAL CHANGES

Pathological changes, typical for foot-and-mouth disease, are found mainly in the oral cavity, the forward sections of the stomach, the extremities, and the udder (the "favorite points"). The parenchymatous organs are also involved to some extent in the pathological process. Localization and intensification of these changes depends on the character of the infection itself and factors which complicate it. In mild, nonmalignant forms of foot-and-mouth disease all these changes do not necessarily involve severe consequences which could in the final sum be reflected on the productivity of the

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animal. However, foot-and-mouth disease does not always run its course in such mild form and, on the other hand, it sometimes leaves after itself very deep pathological changes, often spoiling the animal's value. Particularly serious consequences following foot-and-mouth disease are observed in highly productive and pedigreed animals, which normally develop the disease in severe form if during the period of sickness the necessary feeding and living conditions have not been created and at the same time the essential therapeutic help has not been given.

In literature on the subject, light has been shed in greatest detail on the question of the process itself of the occurrence and the character of development of foot-and-mouth-disease aphthae, and also on the places of their localization in the organism of the sick animal. The foot-and-mouth-disease process, as a rule, develops in the form of a specific exanthema, i.e. with the formation of vesicles or aphthae on mucous membranes of cutaneous type, and also on areas of the skin not covered by hair. On the basis of the experimental data of certain investigators (Akulov and others) it may be considered established that in the foot-and-mouth-disease process mucous membranes of glandular type are also involved.

The atypical form of foot-and-mouth disease described comparatively recently in literature on the subject, with the appearance on the mucous membranes of a "scab" without the formation of vesicles (Cohrs and others), is not typical of this disease and needs further study.

Favorite places of localization of aphthae are the mucous membrane of the buccal cavity and the fore-stomachs, the mucous membrane

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of the throat, the flat fore-part of the nose and the nostrils, and also the skin of the teats and the udder, the coronary band and the region of the cleft of the hooves, the heel, and others. Repeatedly cases have been described of the appearance of aphthae in the region of the anal orifice, the vagina, the scrotum, and elsewhere. In swine aphthae develop on the snout, in the vicinity of the mouth, on the coronary band and heel, the upper hooves, on the feet, on the udder, and on the skin of the belly.

The development of aphthae is accompanied not infrequently by edema reactions and inflammations in the surrounding tissue.

The development of aphthae takes place in the course of 12 to 24 hours from the moment of fixation of the virus in the skin, and in the subsequent 24 to 48 hours after their appearance they rupture, the contents spill out, and the light- or dark-red base of the aphthae is exposed.

Certain investigators (Zschokke, Kern, Föhm, and others) are inclined to connect the appearance of individual outbreaks of foot-and-mouth disease with prolonged survival of the virus inside the hoof (on the sole and walls of the hoof) in convalescent animals. They have found isolated aphthae inside the hoof. The virus, according to Zschokke's statement, and also that of Kern, can survive there for a long time, keeping its virulence, and after wearing of the horn of the hoof be "released" to the outside and become the source of a foot-and-mouth-disease outbreak.

In cattle the most typical changes are observed in the buccal cavity in the form of so-called aphthous stomatitis (Stomatitis

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aphtosa epizootica). The essence of these changes is local inflammation of the mucous membrane accompanied in individual sections by formation of vesicular ("aphthous") exanthema. In the buccal cavity this inflammation can spread to the mucous membrane of the whole buccal cavity; however, most often it is observed on the lip, the ridge, and along the edges of the tongue, on the lips, gums, the hard palate, and the cheeks. The inflammatory process may spread in individual cases from the buccal cavity to the region of the gullet, the pharynx, and the upper respiratory tract, in the latter case in the form of a catarrhal inflammation.

Aphthous stomatitis begins with the appearance in individual parts of the mucous membrane of reddish spots caused by local hyperemia. Somewhat later a gradual scaling of the upper layers of the epithelium takes place on these hyperemic areas of the mucous membrane, and the so-called aphthae form. At first they are the size of a hemp seed, but then they develop gradually to the size of a nut and larger. Aphthae usually are of circular or uneven oblong form, and are of the same color as other areas of the mucous membrane. They fluctuate, first being filled with a transparent serous and slightly yellow-colored content, which at a later stage of development of the aphthae becomes clouded. These aphthae can be located close to each other and merge together. It happens at times that the mucous membrane of the whole lower surface of the tongue is transformed into one continuous vesicle, the size of half the palm of the hand. In goats aphthae on the mucous membrane of the buccal cavity are no larger in size than pinheads, and are often overlooked in practice.

Aphthae form in consequence of an abundant discharge of serous

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exudate from the expanded blood vessels, which separates and raises the upper layer of epithelium (Stratum corneum, lucidum, granulosum and the preserved upper layer of Stratum spinosum), collecting in the vesicles which have formed. The aphthae which have developed soon rupture, often in several hours, usually in 24 to 48 hours after their appearance, in consequence of traumatic damage through the consumption of coarse fodders or simply through motion of the jaws. On the site of the ruptured aphthae dawn erosions with a light-or dark-red base remain. Already by this stage or development of the pathological process a regeneration of the epithelium develops there. Soon at the edges and on the base of these erosions regenerating epithelium appears, and in 6 to 7 days full healing takes place (restitutio adintegrum). At the site of the former aphthae there remains a light region and spots, by which it is not difficult to tell the site of localization of past foot-and-mouth-disease irritations.

According to Ioest, the formation of aphthae on the membrane of the buccal cavity is not only a local process caused by penetration of the virus in that place, but represents the consequence of general infection of the organism as a result of the virus' penetration into the blood and its spread through the entire system. According to Waldmann and Pape, as was indicated earlier, the whole process of development of the infection consists of two phases: in the form of appearance at first of primary aphthae on the place of penetration of the virus, and then of the appearance of secondary aphthae as the result of generalization of the latter.

The pathologo-anatomical changes in the oral cavity described

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here are typical for adult cattle in nonmalignant cases of infection. Depending on the stage of development of the pathological process in the buccal cavity, one may find various changes in the form of unruptured aphthae, erosions, or simply light spots at the sight of past aphthous irritations.

In calves at an early age, particularly when they are still being fed with milk, foot-and-mouth disease most often runs its course in anaphthous form. This is characterized by hemorrhagic inflammation of the membrane of the stomach-intestinal tract, which manifests itself clinically in the form of acute gastroenteritis. At this age parenchymatous changes are most clearly defined in calves. In sheep aphthous irritations are encountered on the toothless edge of the forward jaw, but most often they are observed on the extremities. In goats aphthous irritations are also observed in the buccal cavity, but aphthae and erosions, as indicated, are of very small proportions -- of pinhead size and seldom greater. In swine aphthous irritations seldom occur in the oral cavity, and are most often localized on the extremities and the snout. In sheep and swine aphthous irritations in the oral cavity are much more weakly exhibited than in cattle, and usually run their course without the appearance of drooling.

Together with specific irritations in the buccal cavity many investigators (Uhlrich, Wilhelm, Halfner, Kallert, Ioest, Skomorokhov, Akulov, and others) have observed analogous changes in the forward parts of the stomach, particularly on the mucous membrane of the rumen of ruminants. Nocard and Leclanche point out that on the membrane of the rumen a strong hyperemia, and also typical aphthae and erosions are observed, due to defects in the epithelium in the

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form of softened lumps. Similar indications may be found in Zwick and Fröhner (Fröhner u. Zwick -- Lehrbuch der Speziellen Pathologie u. Therapie, 1925), but these aphthous changes are associated by them exclusively with malignant foot-and-mouth disease.

Kallert observed in foot-and-mouth disease specific changes in the form of erosions on the membrane of the rumen of cattle, which were located along the pillars and were in complete absence on the villous part. These erosions had uneven edges with light-red or grayish-white background, with vestiges of epithelium at the edges. They also observed on the membrane of the rumen spots of various size and shape, of reddish-brown or dark-brown color. On a slide, even with the naked eye it is easy to be convinced that a separation of the upper layer of membrane is taking place here, as a result of which vesicles must subsequently develop.

In Kallert's opinion, the development of aphthae on the mucous membrane of the rumen takes place, in all probability, extremely quickly, since in dissecting foot-and-mouth-disease-infected animals which have been killed it is customary to find all stages of development of specific changes at one time. It is possible that the upper portion of the epithelial membrane, due to movement of masses of fodder in the rumen, bursts very early. Healing evidently takes place on the same principle as in other places, with the formation of new cells from the preserved, unaffected sections of epithelium from the edges or remaining in the middle of the spots. As far as well-developed and unruptured aphthae on the membrane of the rumen are concerned, it is evident from Kallert's description that he did not see them.

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Ioest, in his Spezielle Pathologische Anatomie der Haustiere (1919 Edition, page 332) says that Ruminitis Vesiculosa (aphtosa) is encountered rather often in foot-and-mouth disease. Vesicular exanthema occurs on the membrane of the rumen, which is free of villi, and on other parts it is generally absent. At these places spots of brownish-red or dark-red color are observed, ranging from pinhead size to 1 - 1.5 centimeters in diameter. These spots are round, oval, or irregular in shape. With more detailed investigation these spots turn out to be nothing other than vesicles. Together with vesicles Ioest observed in the majority of cases erosions of uneven shape, not distinguishable in size from aphthae. The base of these erosions ranged from reddish-brown to grayish-white in color. Not infrequently these erosions merge with each other and form considerable blemishes. Erosions can serve, in foot-and-mouth disease, as "entrance gates" for bacilli of necroses and cause the appearance of necrotic centers. The histological picture of the ruminal aphthae in general recalls the histological picture of the aphthae of the buccal cavity.

We have described (1929) aphthous irritation of the rumen in cattle killed at various stages of the disease for the purpose of experimental study. The foot-and-mouth-disease nature of these aphthous irritations was confirmed by means of infection of experimental animals, which method, by the way, is used insufficiently in the investigations of all the foregoing authors. In the cases described,

Figure 7. Aphthae on the mucous membrane of the rumen of cattle (original).

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upon patholoco-anatomical dissection well-defined, unruptured aphthae were observed on the membrane of the rumen along a pillar, of roundish-oval or irregular shape, bluish-red color on the surface and along the edges, and 2 x 1.5 centimeters in size (Figure 7). Upon dissection of one animal 7 aphthae were observed on the membrane of only one pillar. In animals killed at a later stage of the disease, at approximately the same places where aphthae were found earlier in other experimental animals, erosions were observed with sharply defined local inflammatory phenomena and a certain degree of healing (Figure 8). The aphthous irritations described in this case, in the rumen of cattle, coincided in time of appearance with the appearance of analogous irritations in the buccal cavity. Evidently aphthous irritations of secondary as well as primary origin are possible here.

Subsequent patholoco-anatomical dissections of compulsorily killed animals diseased with foot-and-mouth disease have confirmed that the appearance of aphthae and erosions on the membrane of the rumen occurs simultaneously with the development of aphthous irritations in the buccal cavity. The specific changes are doubtless frequently encountered in practice, and not only in malignant, but also in nonmalignant cases of foot-and-mouth disease.

Figure 8. Erosions on the mucous membrane of the rumen of cattle (original).

Later Akulov observed analogous changes on the mucous membrane of the rumen of cattle killed at various intervals of time after

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artificial infection with the virus. He performed 6 pathologo-anatomical dissections. All six head of cattle had developed the disease with complete clinical symptoms of foot-and-mouth disease. The animals were killed 3 to 5 days after infection. Upon dissection multiple erosions were observed on the membrane of the rumen of these animals; these erosions were located along the pillars of the rumen and were of roundish-oval shape with sharp contours of the edges. The surface of just formed erosions was clean, of dark-red color or covered with dirty-yellow exudate. The older erosions were of dark-brown color. The erosions were "atonic" in character. Their size was non-uniform, certain of them attaining the size of a five-kopek piece, no more than 0.3 to 0.5 centimeters in depth, and in no case penetrating to the muscular layer of the pillars of the rumen.

Akulov also dissected 2 head of cattle killed on the 12th to 13th day following appearance of primary aphthae in the buccal cavity. Upon dissection there were observed on the mucous membrane of the pillars of the rumen individual round-shaped, light-gray spots, somewhat raised above the surrounding surface. Upon histological investigation it turned out that these were nothing other than regenerated aphthae. We have succeeded (1936) in observing, on the membrane of the rumen of a cow killed compulsorily in another connection, multiple erosions on the 21st day following development of the disease, when the animal was considered fully recovered from foot-and-mouth disease on the basis of clinical data. In this case there was an aphthous process of sharply defined character. It is possible that such cases of atonic phenomena in aphthous irritation of the rumen are no longer of such rarity, but unfortunately they

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have not yet been studied. Consequently, at the present time it may be considered conclusively established that, together with aphthous irritation of the mucous membrane of the buccal cavity, analogous changes take place also on the membrane of the rumen with malignant as well as nonmalignant cases of foot-and-mouth disease. All these stages of development of the aphthous process evidently occur simultaneously with aphthous irritations in the buccal cavity.

As to what degree and how often all the other organs of the digestive tract are involved in the foot-and-mouth-disease process, there are very sparse indications available in existing literature. Nocard and Leclainche adduce the following data with respect to irritation of the other organs due to foot-and-mouth-disease infection: the mucous membrane of the omasum is pale, and at various points dark-red spots representing diffuse capillary hyperemia or hemorrhage in the submucous membrane are observed. The mucous membrane of the abomasum and the small intestines is inflamed, almost red in color, and covered with dark-brown spots and hemorrhagic spots, and the submucous layer shows the parent infiltration.

The mucous membrane of the rectum is inflamed and ecchymotic. According to other authors (Ulbrich, Wilhelm) centers of necrosis, as an exception, are observed on the edge of the folds of the omasum. Incidentally, as early as a report of an English commission dating back to 1666 necrotic irritations of the omasum are mentioned and drawings are given (Nocard and Leclainche, "Microbe Diseases of Animals", Vols. I and II, published by "The Archive of Veterinary Science", 1908).

According to Kallert, the mucous membrane of the abomasum and

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intestines in foot-and-mouth disease is dark red in color with numerous small hemorrhages. According to Ulrich, several deep ulcers or dark-brown scabs with slightly raised edges are observed rather often in the abomasum on the folds of membrane. On the mucous membrane of the small intestines certain authors have noted pinpoint hemorrhages in the shape of narrow and diffusely colored bands. Similar changes are described by many authors, mostly for malignant foot-and-mouth disease.

Foot-and-mouth-disease sickness very often involves disorders in the action of the heart as a result of profound damage to the cardiac musculature. Many investigators connect these changes with the malignant form of the infection; however, even in nonmalignant cases analogous changes are fairly frequent. According to the data of Schmidt, who investigated 300 cattle hearts, in nonmalignant cases of foot-and-mouth disease temporary changes in the cardiac musculature were noted in 3 percent, and in 0.67 percent permanent changes remained in the form of cardiac scars due to deeper irritations. The author is inclined to ascribe all these changes in the cardiac musculature to the specific effect of the virus.

Kitt, Johne, and also Nocard, first devoted attention to these changes in the heart muscles and classified them as specific changes caused by foot-and-mouth disease. In examination with the naked eye the heart muscle appears pale and flabby, with grayish-red, grayish-white, or, finally, grayish-yellow spots scattered on the surface of the section, the size of a corn kernel or slightly larger. Such unique spotting of the heart muscle led to its being called "tigerish" (Kitt). These changes can be observed in the depth of myocardium, in

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the cardiac wall, or in the wall of the left or of both ventricles of the heart. Together with small, scattered spots certain investigators have observed in the myocardium of the auricle, in the cardiac wall, or in the wall of the left ventricle changes in the form of small foci of irregular shape. These foci are softer in consistency by comparison with the surrounding parts of the myocardium. Akulov observed similar changes in two calves which had died from malignant foot-and-mouth disease. In the cases which he described he observed in the myocardium of the left ventricle caseously regenerated foci of grayish-white color, ranging in size from that of a corn kernel to that of a nut. The specific character of these changes is not in doubt at present; however, their pathogenesis remains the object of little study so far.

Changes in the heart muscles occur in the parenchyma itself, as well as in the interstices (Ioest). The essence of the parenchymous changes is the atrophying of the muscle fibers either in the form of ordinary, simple atrophy or in the form of fatty degeneration. Akulov observed mainly parenchymatous changes in calves which had died of malignant foot-and-mouth disease, and in adult cattle (in nonmalignant cases -- A. S.), on the other hand, interstitial inflammation with slightly protruding irritations of the parenchyma predominated.

This whole process was characterized by Ioest as miocarditis acuta multiplex, and by Schlegel as miocarditis necrotica multiplex. The reason for the appearance of focal changes in the heart muscles is seen by many investigators in the toxic effect of the virus (Bol' and Agul'nik, Ivanov and Akulov, Bol' and Akulov, Ioest, Schminke, and

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Miessner). Nieberle considers that the myolithic process occurring here is caused by the action of specific toxins of the virus, and the inflammatory phenomena occur later, due to the poisonous products of decay released in the process of myolysis (Hutyra and Marek, "Special Pathology and Therapy of Domestic Animals", Vol. I, 1933, page 416). This statement of Nieberle's needs further investigation and substantiation.

According to the data of Nieberle and Menkeberg, and also of Bergmann, Schlegel, Zschokke, and others, the primary processes have a manifest degenerative character, while in the beginning stages they always observed the processes of parenchymatous degeneration only, with an inflammatory reaction coming later. Waldmann and Trautwein, in investigations of calves' hearts, found, on the other hand, a predominance of inflammatory changes. Akulov, in his investigations into changes of the heart muscle of adult cattle and calves, observed a predominance in one case of degenerative, and in another of inflammatory changes. He assumes that both these processes (degenerative and inflammatory) can take place simultaneously. Many authors, in investigating acute focal miocarditises, especially in calves, note among the degenerated muscle fibers the presence of grains of lime phosphate (Markus, Ronca, Wester, Ericon, Schmidt, and others). Lenkeit regards the calcification of the heart muscle in calves as a productive process. Schmidt discovered in one bull's heart a calcification of the muscle fibers.

In the histological investigations of changes in the cardiac musculature performed by numerous investigators (Kitt, Johne, Nocard, Iocst, Markus, Ronca, Nieberle, Schlegel, Bergmann, and others) a

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focal hyaline regeneration and falling to pieces of the muscle fibers are observed, with subsequent small-celled infiltration of the interfibral spaces (Ioest), there being simultaneous proliferation of the muscle nuclei (Wester) and spreading of the connecting tissue. (Hutyra and Marek. "Special Pathology and Therapy of Domestic Animals", Vol. I, page 416.) Schmidt, in histological investigation of the heart muscles found a rather uniform picture of focal changes. It consisted of spreading of the connecting tissue in the interstices, a more or less considerable quantity of fatty cells and elastic fibers being found in the tissue (Figure 9). In other areas the spreading of the connecting tissue spread also to the muscle fibers, which was preceded by degenerative changes (Figure 10). The presence

Figure 9. Spreading of the connecting tissue and accumulation of fatty cells in the interstices of the heart muscle (after Schmidt).

Figure 10. Development of the connecting tissue in the heart muscle (after Schmidt).

of the virus in these foci Schmidt could not prove; however, the scars and "horny" thickenings observed by him in the heart are, in the author's opinion, unconditionally the result of previous myocarditis (Figure 11) (Similar infections are seldom encountered in other infectious sicknesses.)

Schminke described a focal leucocytic and fibroblastic infiltration of the perimysium with a predominance of polynuclears

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among the cellular elements. In individual cases the authors observed a hyaline-lumpy process and very infrequently a fibrillar collapsing of the muscle fibers. Zschokke observed myofragmentation with a liquefaction of the Kitt's substance of the muscle fibers. Similar changes have been described by many investigators (Haak, Puschli, Sluis, Giovanioli, and others); however, their origin needs further scientific study. In general, aphthous myocarditis must be considered a rather frequent phenomenon in nonmalignant cases of foot-and-mouth disease, too (Cochini, Schmidt, and others). Myocarditis of aphthous origin is very often accompanied by interstitial and parenchymatous changes (Cochini). In the event of recovery scars due to the development of connecting tissue appear on the site of focal changes in the cardiac musculature.

Figure 11. An inflamed focus of the myocardium with incipient scarring of the connecting tissue.

Aphthous myocarditis involves very deep functional disorders on the part of the heart, and not infrequently leads to the animal's death.

Various complications are evidently possible, too, as a result of irritation of the heart muscles; these complications can manifest themselves considerably later. Barrat observed in one bull, as the result of foot-and-mouth disease, an abscess in the heart muscle. Upon dissection he discovered in the cardiac wall an abscess the size of a hen's egg, filled with a white pus like sour cream. A second such abscess turned up in the wall of the left ventricle. The heart

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muscle was pale and discolored in spots. The bull had developed foot-and-mouth disease earlier, 5 months before dissection. His death had occurred suddenly. The reason for death was myocarditis.

Tolstova-Pariyskaya, in dissection of calves which had perished from foot-and-mouth disease, observed (personal communication of the author) a case turbidity of the bicuspidate, less frequently of the tricuspid valves of the heart, not infrequently with hemorrhagic infiltration of them and formation between the folds of the endocardium of limited hemorrhagic foci of hematic type.

The pathologo-anatomical changes of the other organs and systems have been almost absolutely unstudied. There is a particular source of interest in changes in the nervous system, in connection with the description by certain authors of nervous forms of foot-and-mouth disease (Terni). No less interesting is the problem connected with the determination of the neurotropic character of the virus. Levaditi, Galloway, and Nicolau consider that the nervous system is not affected by foot-and-mouth disease. Loest, in investigating the Purkinje cells, found no specific changes. Mankenberg, and also Semmike, on the other hand, observed degeneration of the nerve tissue together with irritation of the muscles. Gins and Krause, Bergmann, Wester, and Zschokke also observed irritation of the cardiac nerves, which they ascribed to the specific effect of the virus. Ivanov and Akulov, on the basis of their investigations, reached the conclusion that the nervous system is doubtless affected. On the basis of the data given it is possible to consider it proved that the nervous system is involved in the foot-and-mouth-disease process and in severe forms of infection undergoes considerable changes. As far as the neuro-

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tropic properties of the virus are concerned, their verification is found in the research of Levaditi, Nagel, and others, who succeeded with passage of the virus in the central nervous system of laboratory animals.

Numerous data of different investigators point to the fact that the skeletal musculature is also affected. These changes are localized in large animals, mainly in the muscles of the hip and shoulders. In malignant cases of foot-and-mouth disease in guinea pigs as the result of experimental infection the skeletal musculature is affected throughout (Ivanov and Akulov). In external appearance the changed muscles of large animals usually recall fish meat (Semmikе). The basis of these changes is in the same inflammatory and degenerative processes. Degeneration of the muscle tissue is accompanied by small-cell infiltration of the interstices and falling away of the hyaline (Pernice and Roggio). Squadrini observed similar changes in the skeletal musculature of adult cattle (3.66 percent) and calves (5.5 percent). In histological investigation these were established: myosis, wax-like degeneration of the sarcoplasm, and coagulative necrosis with depositing of lime.

Akulov, and also Ivanov and Akulov, performed research into exchanges of the trachea, lungs, liver, kidneys, suprarenals, glands (pancreas, salivary and lymphatic ganglia), spleen, brains, and peripheral nervous system. They reached the conclusion that the most typical form of reaction to the effect of the virus is in the processes of swelling and vacuolar homogenization, and degeneration and thinning of protoplasm. In irritation of the mucous membranes of glandular type and certain parenchymatous organs the cause is the same

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process of serous inflammation as in the mucous membranes of cutaneous type. Akulov separates all changes in foot-and-mouth disease into two groups, of which the first occur with inflammatory phenomena (changes in the mucous membranes of the cutaneous and glandular type, changes in the lungs, and in the liver), and the others have the character of degenerative changes (muscles, suprarenals, pancreatic gland). All questions touched upon by this author in his investigations are in need of still more detailed study, in order that final conclusions may be drawn on them.

A process analogous to that in the buccal cavity develops on the skin of the extremities in the region of the cleft of the hoof, the coronary band, and the heels, i.e. aphthae and erosions appear there, but their healing takes longer. The aphthous process in these places can be primary as well as secondary in origin as the result of generalization of the infection.

Krause, on the basis of pathologo-anatomical changes, distinguishes three characteristic forms of the foot-and-mouth-disease process: (1) simple derma-aphthous, (2) septic or toxic-aphthous, (3) myopathic or cardiopathic. The latter, i.e. cardiopathic, form usually runs its course without formation of aphthae, causing severe disorders in the circulatory system and often having a complex outcome.

Study of the histology of the aphthous process has engaged very many investigators (Kitt, Terni, Zschokke, Boehm, Ioest, Kallert, Waldmann, Ernst, Krause, Levaditi, Bol' and Agul'nik, and others). The histological picture of the aphthous process in the buccal cavity, the rumen, and also the extremities and the udder, is generally uniform. Kallert, moreover, observed in aphthae of the rumen bleeding in the

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Stratum spinosum. This phenomenon is evidently seldom encountered. The histological picture, and also the development of the aphthous process, are in general uniform in cattle as well as in swine and guinea pigs, and evidently in all remaining animals susceptible to foot-and-mouth disease.

Pathologo-anatomical changes in malignant foot-and-mouth disease have so far been inadequately studied. Scientific data available on this question are extremely varied, and therefore it is difficult to decide what must be ascribed to the specific action of the infection and what are accidental, concomitant changes. As the most constant phenomena in malignant foot-and-mouth disease in adult cattle are the various foci and degenerative changes and, in addition, hemorrhagic gastroenteritis in calves. In a malignant case of foot-and-mouth disease in guinea pigs Bol' and Agul'nik observed acute parenchymatous inflammation of the muscle tissue of the heart with a tendency toward focal development and necrosis. According to the affirmation of these authors, these changes in the heart muscle have the same character in large animals, too.

Skryab'n has provided a detailed description of pathologo-anatomical changes in the anaphthous form of malignant foot-and-mouth disease of cattle. According to his observations, upon dissection

Figure 12. The rumen of cattle affected with malignant foot-and-mouth disease. An ulcer of the rumen at the boundary between the pillars and the villous part. A recent-ulcer type, surrounded by a raised surface without disintegration in the center (after Skryabin).

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of the first section of the stomach ulcerations of various size are clearly distinguished, sharply contrasted with the underlying tissue (Figure 12). The ulcers were observed on the pillars of the rumen exclusively. At the same time they were absent in places covered with villi. The ulcers were of "atonic" character: no reaction was perceptible on the part of the underlying tissue, and the tissue of the pillars of the rumen appeared completely normal. There were 2 of them of various sizes and shapes and different stages of caseous regeneration. The smallest ulcer had a diameter of 14 millimeters, and the largest was in the form of an uneven ellipse with major axis equal to 4.5 centimeters, and minor axis 25 millimeters. The ulcers were of roundish-oval form with unusually sharp contours and surfaces somewhat raised above the surrounding tissue by edges of horny character. A horny ring was clearly perceptible in the young ulcers. The surface of the young ulcers appeared even, and relatively flat, consisting of layers of a rather hard clotted coating of dark-grayish color with a greenish tinge. The deep layers were lighter. The old ulcers seemed to be in the last stage of caseous regeneration and were filled with a semifluid mass reminiscent of sour cream (Figure 13). The ulcers were up to 1 centimeter deep, penetrating into the muscle layers of the pillars of the rumen. The base of the

Figure 13. Ulcer of the rumen of cattle in malignant foot-and-mouth disease. The ulcer of the rumen of a calf in the middle of a pillar. A "ripe" ulcer with caseous disintegration in the center (Skryabin).

ulcers appeared uneven with a solidly attached caseous disintegration.

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The ulcers described by Skryabin appear completely analogous to ulcers in the bucral cavity of the same animal; their character is one and the same, and the only thing different is the tissue base on which they developed. In this case they were the "aphthous" ulcers of the stomach of ruminants. These pathological changes were observed in a two-year-old heifer, which had suffered the typical "non-pustulent" ("non-aphthous" would be more correct) form of foot-and-mouth disease with atonic ulcers of sharply defined character in the buccal cavity, and had died following two weeks of almost complete lack of nourishment. Skryabin observed a second case with similar irritations in a year-and-a-half-old bull calf, but at an earlier stage of the development of the infection. In this case the ulcers were not limited only to the region of the pillars of the rumen, but were scattered throughout the whole rumen, attacking the villous part of the rumen as well as the pillars.

Skryabin, in addition, described specific irritations on the reticulum. On the reticulum, not far from its boundary with the omasum, he observed a dark spot of uneven round shape, 2.5 centimeters in diameter, in whose center the cavity of a cell was filled with a clotted

Figure 14. Necrotic foci on the mucous membrane of the omasum of cattle. Necrosis of the folds of the omasum. The upper portion of the central fold in the drawing is without changes, with normal cone-like nipples. The lowest part of the drawing corresponds to the transition from the omasum to the reticulum (after Skryabin).

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mass. The caseous disintegration of the centers of the ulcer was relatively dense in consistency, since the process had evidently been fairly recent. Around this biggest ulcer there were situated fairly nearby two smaller ulcers, which had affected only two cells of the reticulum. On the omasum the process had affected the free edges of the folds located on the boundary with the reticulum (figure 14). Beginning there and proceeding in the direction of the cavity of the omasum, continuous necroses of the tissue of the folds, up to or 7 centimeters in length, were noticed on six folds. Necrosis had in these places attacked the whole thickness of these six folds up to the reticulum itself. The necrotic areas were of greenish-gray color, completely like that of the irritated sections of the rumen. On a slice-section the necrotic tissue appeared to be homogeneous up to the base of the folds itself. The base of these ulcers was uneven and had an "atonic" character. Skryabin simultaneously described specific changes of the esophagus (figure 15). In the region of the pectoral section of the esophagus the mucous membrane was a picture of acute inflammation, being hyperemic, intensely red in color, with a violet-slate tinge in places. The surface of the

Figure 15. Necrotic foci on the mucous membrane of the esophagus of cattle with malignant foot-and-mouth disease. Erosions on the mucous membrane of the esophagus. At bottom left are noticeable whitish membranes covering erosions. At center left dark erosions are visible (after Skryabin).

membrane on the whole affected area was studded with protruberant whitish islets -- films which had attached to the underlying tissue,

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of uniform size and elliptical shape. Under this whitish film was revealed a corrosive ulcer in the form of a hollow -- a typical erosion, reminiscent of erosions in the throat, at the root of the tongue, and elsewhere with cattle plague. All these changes were observed in just those animals for whom ulceration of the rumen had been established; while the ulcers on the rumen were of sharply "atonic" character, without any hyperemia of the surrounding parts, the inflammation of the esophagus bore a clearly acute character.

The anaphthous form of foot-and-mouth disease (non-pustulent foot-and-mouth disease) was evidently first described by Pavlov (1873). On the mucous membrane of the buccal cavity, in those places where aphthae usually appear, he observed small nodules which were quickly transformed into "light cheese-like layers easily separated from the mucous membrane, which upon their removal present a smooth, red surface". This was the degenerative process of disintegration of the epithelium (albuminal, fatty regeneration).

Shadrin (1891) observed an epizootic of foot-and-mouth disease which ran its course in atypical form without formation of aphthae, but with formation of clotted films on the mucous membranes. Similar changes with the atypical form of foot-and-mouth disease were observed by Mikhaylov, and also by Korsak, although they observed characteristic development of aphthae simultaneously with the clotted coverings. The reasons for the appearance of the anaphthous form of foot-and-mouth disease have not been studied.

Terni (1915) described a nervous form of foot-and-mouth disease, in which he found the following pathologo-anatomical changes: clearly manifested hyperemia of the marrow membranes and marked

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increase in the cerebrospinal fluid, rich in albumins. These changes are evidenced most acutely in comatose form, during which, together with the changes described, focal hemorrhagings in the web-like membrane are noted. Other pathologo-anatomical changes with this form of malignant foot-and-mouth disease are either completely lacking or are not typical. Similar changes are usually found in calves which have died from malignant foot-and-mouth disease.

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CHAPTER V

THE CLINICAL PICTURE OF FOOT-AND-MOUTH DISEASE

GENERAL DATA

Foot-and-mouth disease represents a unique exanthema, appearing in the form of a vesicular eruption on the mucous membranes and parts of the skin not covered with hair. Specific irritations are noted mainly in those parts of the animal's system which are exposed to spontaneous stimulation, and also not infrequently to damage (ernst). In these places absorption of the virus evidently takes place in the corresponding susceptible ("receptive") tissues. This process occurs on the site of penetration of the virus into the animal's system, and manifests itself in the form of primary aphthae, and also, during subsequent generalization of the infection, the appearance of secondary aphthae. With this the localization of the foot-and-mouth-disease process in definite places in the animal's organism is evidently explained.

In almost all animals susceptible to foot-and-mouth disease the "favorite places" for localization of the foot-and-mouth-disease process are, as will be seen later, the mucous membrane of the buccal cavity, and also the skin in the region of the coronary band and the heels on the extremities, and finally the skin of the udder, with occasional exceptions as to the intensity of development of the pathological process. The development of the infectious process in all animals naturally susceptible to foot-and-mouth disease runs its course with rather well-defined clinical symptoms of the disease, which

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can be brought to light and studied with the help of the methods of clinical research.

In conditions of natural spread of foot-and-mouth disease the course of the disease is almost always acute and unprolonged. The less acute ("mild") form of the disease, indicating usually an increased resistance of the animal's system to foot-and-mouth-disease infection, is encountered relatively seldom. Among adult animals the so-called abortive form of the disease is observed at times. In this case the disease runs its course with brief, inconsiderable increase in temperature and rapid recovery. In individual cases symptomless forms of foot-and-mouth-disease sickness are also possible (Mouse and others), which in natural conditions of development of the foot-and-mouth-disease epizootic is very seldom observed.

Young animals (in the milk period) develop foot-and-mouth disease somewhat differently, specifically, as noted earlier, in anaphthous form, accompanied by a high percentile mortality.

In conformity to contemporary scientific data relating to questions of the pathogenesis of foot-and-mouth disease, the appearance of clinical symptoms of the disease must be regarded with consideration of the two-phase character of the development of the foot-and-mouth-disease process. In the first phase primary aphthae on the site of penetration of the virus cannot always be observed with the help of clinical methods of research, and therefore this stage of development of the disease very often remains clinically unilluminated and undiscerned. In the second phase, with the coming of generalization

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there appear secondary, plural aphthae and at the same time there develops a whole set of other clinical phenomena typical of foot-and-mouth disease. Individual cases of foot-and-mouth-disease sickness are also possible without generalized infection, when the whole foot-and-mouth-disease process is limited to appearance of only primary aphthae on the site of penetration of the virus. In such cases the disease runs its course very mildly and quickly terminates in recovery.

The incubation period in foot-and-mouth disease, as in other acute infectious sicknesses, is not prolonged. The higher the sensitivity of the animal's system at the moment of infection, the greater the "infectious" dose of virus, the stronger its virulent properties, and finally the more favorable the tissue medium into which the virus penetrates upon infection of the animal's system -- the shorter the incubation period. The length of the incubation period in foot-and-mouth disease can be affected by external factors which have an unfavorable influence on the general condition of the animal's system. Roemmele affirms, for example, that high temperature of the surrounding air (not summer) shortens the length of the incubation period and causes a more severe case of the infection.

Many investigators (Lignieres, Allendorf, Roemmele, and others) consider that with low temperature of the surrounding air, on the other hand, the incubation period is more lengthy, and the course of the infection more mild. The author and his colleagues have been repeatedly convinced of the accuracy of these observations. Foot-and-mouth disease in wintertime, as is well known to veterinary doctors and workers in the field, is much milder and usually without the severe

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complications which are so often observed during summer foot-and-mouth-disease epizootics.

However, under all conditions the length of the incubation period is more or less constant with inconsiderable fluctuations in one direction or the other.

From the practical standpoint it is very important to know that virus from the organism of an infected animal begins to pass into the surrounding air right in the incubation period of the disease. In the prodromal period, when specific symptoms still continue to be absent, the virus passes into the surrounding air in enormous quantities and has also an extremely high virulence. Animals in the incubational and prodromal periods of the disease represent an exceptionally great danger from the standpoint of scattering of the virus in the surrounding medium.

THE CLINICAL PICTURE OF FOOT-AND-MOUTH DISEASE IN CATTLE

The incubation period in cattle in conditions of natural foot-and-mouth-disease infection lasts an average of 2 to 4 days (Waldmann). According to the data of other investigators it lasts an average of 2 to 6 days (Marms and others), and in exceptional cases even considerably longer -- up to 11 days (Sidamgrotskiy and Bern), up to 14 days (Schrader), up to 17 days (Berens), up to 21 days (Isseponi), and up to 27 days (Bürgi). The minimum period of incubation in foot-and-mouth disease in conditions of natural infection is considered by some investigators to be 36 hours (Schutz) and by others 24 to 48 hours (Fröhner and Zwick). The maximum period of incubation,

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nevertheless, must be held to be 7 to 14 days (Pröhner and Zwick, and others). On the basis of experimental data it may be assumed that there are even shorter periods of incubation -- 24 hours and even 12 hours (Hoeard and Leclainche). Harms describes a case of sickness in one cow with clinical symptoms 36 hours after she was placed in a building where there had previously been animals sick with foot-and-mouth disease. In experimental infection, depending on the method and place of injection of the virus into the organism of the animal, the length of the incubation period can be very short or, on the other hand, prolonged.

In our experiments on cattle with intracutaneous injection of the virus the incubation period comprised 14 to 15 hours in all. Waldmann, in infection of cattle in the mucous membrane of the buccal cavity, observed in individual cases an incubation period of 15 hours and more in length. According to Schutz' data, the length of this period in experimental infection comprises an average of 40 to 50 hours.

With intravenous injection of the virus in cattle the incubation period can last from 6 to 120 hours from the moment of injection of the virus (Loeffler and Frosch).

The incubation period is replaced by the prodromal, and at that time general symptoms of ~~advancing~~ already present foot-and-mouth disease appear in the form of a reduction in the desire for fodder, a somewhat slowed-up rumination of the cud, a small flow of saliva from the oral cavity, and an inconsiderable decrease in milk yield. These symptoms are often so weakly pronounced that they are frequently not noticed in practice. The first specific symptoms of foot-and-mouth-disease sickness usually

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become noticeable only after clearly pronounced development on the site of penetration of the virus of a primary aphtha, when this aphtha ruptures, and immediately afterward generalization of the infection comes.

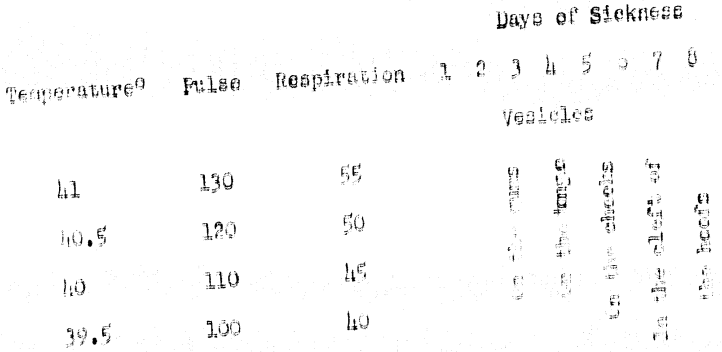

Figure 16. Temperature curve for a typical case of foot-and-mouth disease in cattle.

In the period of the first phase of development of the foot-and-mouth-disease process, in spite of the absence of clearly pronounced symptoms of sickness -- general as well as specific -- it is possible with extremely elaborate and attentive clinical examination of the animal to discover the primary aphtha. There are normally one to two of them, and very seldom more. However, specific symptoms of

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foot-an-mouth disease are clearly pronounced only with the coming of generalization of the infection, i.e. with the beginning of the virus' entry into the blood and its distribution throughout the entire system.

In the period of the second phase of development of the foot-and-mouth-disease process general symptoms of disease manifest themselves together with specific symptoms: temperature rises to 40.5 - 41.5 degrees, a strongly pronounced depressed condition is noted, the pulse increases, the respiration increases, and then the animal refuses fodder and the cud ceases altogether. The sick animal usually stands motionless, with head lowered, and from the corners of the mouth viscous and foamy saliva stretches in long threads. During this the mouth is closed at all times; upon opening of the mouth a unique "smacking of the lips" takes place (evidently the result of sticking of the tongue to the hard palate). This condition

Figure 17. Aphthae and erosions on the mucous membrane of the oral cavity (after Hutyra and Marek).

is preceded by strong hyperemia, dryness, and soreness of the mucous membrane of the buccal cavity. With the appearance and rupturing of secondary aphthae the temperature falls back to normal, which is evidently connected with the disappearance of the foot-and-mouth-disease virus from the blood, and does not again rise if the illness is not further complicated by other septic processes.

Upon examination of the buccal cavity at the very beginning of the disease, when the first symptoms of sickness have already

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appeared, but generalization has not yet come, it is possible to observe at times on the mucous membrane of the tongue, the gums, and the upper or lower lip one or more primary aphthae at the site of penetration of the virus. They attain considerable proportions at times -- the size of a nut and larger. With the advancement of generalization of the infection, which coincides in time with the moment of rupturing of the primary aphthae, secondary or plural aphthae appear in the buccal cavity, on the extremities, and on the udder. They usually appear on the second or third day of the sickness, being observed on the inner surface of the upper and lower lips, on the toothless edge of the lower jaw, on the dorsal part, the edges, around the base, and on the bottom muscular part of the tongue, and also on the inner surface of the cheeks (Figure 17). At almost the same time or somewhat later secondary aphthae appear on all remaining susceptible ("favorite") places.

Figure 16. Erosions on the mucous membrane of the tongue of cattle (original).

At the very beginning of development the secondary aphthae have the form of small formations the size of a corn kernel, then soon reach the size of a pea, and finally, developing further, attain the size of a walnut and even larger. When these aphthae merge together, one or several larger aphthae are formed. Such consolidated aphthae occur most often on the tongue. After the aphtha has reached full development, it usually ruptures in 12 to 24 hours, leaving behind it fresh erosions (Figure 16). Erosions after primary as well as secondary aphthae are rather rapidly, in 2 to 4 days, covered with regenerated

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epithelium. Fresh erosions are at first covered with a dirty yellow film, and then the formation of new epithelium takes place beneath the film.

Regrowth of the epithelium begins from the edges or from the "islets", if such have been preserved. On the second to the fourth day following appearance of the erosion, and still earlier with the abortive form, they are already covered with new epithelium, leaving dark-gray and yellowish-brown spots, which disappear without a trace with the passage of time. Full regeneration of the tissue on the place of the erstwhile aphthae and erosions can last considerably longer -- up to 2 or 3 weeks at times -- with a harsh case of sickness or poor condition of the animal. With healing of erosions in the buccal cavity the animal again takes feeding.

According to Ozerov's observations, the temperature of a sick cow in the period of formation of aphthae reaches 40.4 - 40.9 degrees and even 41.2 - 41.5 degrees. High temperature continues for 2 to 3 days usually, extending at times up to 5 and even 10 days, with various fluctuations, as a consequence of complicating factors.

Figure 19. Foot-and-mouth-disease irritation in the region of the rim of the hoof of cattle (original).

The appearance of primary and secondary aphthae, and then the formation of erosions and their healing, as a rule occur with strongly pronounced salivation, almost complete refusal of fodder, and disorder of other functions of the system. As a consequence of all this strong emaciation and loss in weight of the animal take place. With irritation

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of the buccal cavity sick animals dip their mouths into water. Not infrequently intensive thirst can be noted in them. With irritations of the stomach-intestinal tract and especially with aphthous irritation of the rumen in sick animals, as indicated earlier, diarrhea and constipation are observed.

Almost simultaneously or somewhat later than the formation of secondary aphthae in the buccal cavity similar aphtha appear on the hide of the coronary band and heels in the region of the cleft of the hoof (Figure 19). The sickness usually begins with the appearance in these places of an at first irritated and painful swelling, accompanied by strong discoloration of the skin (if it is not pigmented). At the very beginning of the disease in the extremities the animal begins to shift frequently from foot to foot, extends its hind legs -- first one, then the other -- and shakes them. Then difficulties in the gait appear, and the animal begins to limp strongly on the most irritated extremity, and with irritation of two or all four of the extremities lies down all the time and can raise itself onto its legs only with great difficulty. Upon pressure exerted in the region of the cleft of the hoof, and particularly on the coronary band and heels, the animal quickly and sharply withdraws the painful extremity. In 24 to 48 hours on the place of the irritated and painful tumor aphthae appear, which, like aphthae in the buccal cavity, soon rupture, and the contents pour out. On the site of these ruptured aphthae very damp and painful erosions remain, quickly becoming covered with a grayish film. Under this film, in the form of scabs, a rather slow regeneration of the epithelium and healing of the erosions occur, which in individual cases can last for

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one or two weeks and even longer.

According to Ozerov's observations (1924 - 1926), the duration of the disease in cattle can run in mild form from 3 to 5 days, in more severe form from 7 to 8 days, and in severe cases with complications from 12 to 15 days.

With affliction of the extremities all four extremities are usually affected simultaneously, or only both forward or both rear extremities. This takes place most often in consequence of generalization of the infection and "settling" of the virus in the most frequently irritated parts of the extremities (on the skin of the coronary band and the heels). Cases of affliction of the remaining extremities are possible, however, when the virus penetrated directly into damaged tissue of a given extremity. At the site of penetration of the virus a primary apitha develops, which in turn is accompanied by inflammatory phenomena, pain, and limping of the animal. Affliction of the extremities, particularly at the beginning of the disease, is always accompanied by pronounced limping. In the period of convalescence, in consequence of interruption of the growth of the horn of the hoof, a flaw is formed between the old horn wall and the newly formed horn, into which dirt, manure, and sand fall. Because of this there usually begins a purulent process with the formation of abscesses, and in severe cases the shoe part of the hoof falls off. The abscesses break outwardly, or the purulent process spreads deep down and, as a consequence of this, there occur at times carious processes, and necroses of the coronary and hoof bones. As a result of disease of the hoofs so-called "double soles" and cracks in the hoofs are formed.

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With good care and condition of the animals and correct treatment all these severe complications can be prevented, and then the whole process associated with affliction of the hoofs lasts no longer than 7 to 14 days, leaving no more or less noticeable consequences behind it.

Zschokke observed aphthae inside the shoe part of the hoof between the horn and the skin, in which the virus, in his opinion, had remained hidden for a long time and was released externally upon wearing or cutting of the hoofs. These hidden aphthae can unite with aphthae in the region of the cleft of the hoof and in the region of the heels, and along this path the virus can be transmitted externally. Zschokke himself recognized the very significant epizootological importance of this fact of the survival of the virus in hidden form in the shoe part of the hoof. Outbreaks of new epidemics through the introduction of animals which have had foot-and-mouth disease into an uncontaminated herd were explained by him by the survival of the virus inside the shoe part of the hoof. Zschokke assumed that the virus in such cases can survive for many months. This also, in his opinion, explains the cases occasionally observed of lameness in the absence of any specific external irritations whatsoever of the extremities.

Many authors (Böhm, Hess, Conradti, Bürgi, and others) share Zschokke's views on this question, although later experimental investigations (Brandt) have not verified his conclusions. Zschokke's data lack adequate experimental foundation and do not have, in our opinion, serious practical significance for the epizootology of foot-and-mouth disease.

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In cows the udder, particularly during the period of lactation, is very often affected. Aphthae and erosions appear on the teats (Figure 20). The aphthae are of irregular shape and non-uniform proportions, at times attaining the size of a nut. During the first milking the aphthae usually rupture and in their place damp, painful erosions remain, quickly becoming covered with yellowish-brownish scabs. On the site of the developing aphthae redolsnness, slight swelling and painfulness, and then a vesicle appear at first. Not infrequently the apertures of the teats are also affected, which can involve stoppage of the teats by the scabs which form.

In spread of the inflammatory process from the affected teats of the udder to other, deeper-lying tissues various complications and abscesses are possible together with inflammation of the udder, due to penetration of microbes from the surrounding atmosphere. The appearance of aphthae on the teats is not infrequently accompanied by catarrh of the lactary canals. The composition of the milk is altered, and secretion is abruptly decreased. The milk becomes slimy and yellowish like colostrum, is bitter to the taste, acquires acidity, curdles very easily, and is difficult to churn into butter. At times "blood streaks" appear in the milk. Following recovery of milk cows, the amount of milk production rarely returns to the previous standard.

The quantity of milk decreases substantially with irritation of the udder, which, however, occurs during foot-and-mouth disease even in the absence of specific irritations. The composition of the milk also changes considerably with foot-and-mouth disease.

Figure 20. Aphthae and erosions on the teats of a cow's udder (original).

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Specific irritations in cattle are at times observed on the mucous membrane of the nasal cavity, about the flanges of the nose and on the muzzle (Ozerov, Skomorokhov, and others), and also, although infrequently, in the region of the anus and the vagina.

Ozerov observed in one young bull aphthae on the skin at the very base of the horn, which occasioned falling off of the horn. Similar phenomena have also been repeatedly noted before by certain foreign authors.

Not infrequently disorders of the functions of the stomach-intestinal tract are observed, mainly in the form of diarrhea (Ozerov, Skomorokhov, and others). In the young of cattle and sucking pigs foot-and-mouth disease, as has already been indicated, usually runs its course in anaphthous form with symptoms of diarrhea. In such case these clinical phenomena are most often the consequence of a specific irritation of the membrane of the stomach-intestinal tract. This anaphthous form of foot-and-mouth disease in calves usually ends in death if measures are not taken for the provision of timely therapeutic help.

Many investigators, as already indicated earlier, have described specific irritations on the mucous membrane of the rumen of cattle, analogous to the changes which are observed in foot-and-mouth disease on the membrane of the buccal cavity.

During one epizootic Ozerov observed in a cow a membrane-pus efflusion from the nose.

Development of foot-and-mouth disease by cattle not infrequently

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involves temporary or permanent disorders of the cardiac activity (missing, filiform pulse, and others). Schmidt performed a clinical observation of cattle exposed to thrice-repeated infection. As a result, in 13.7 percent disruptions of cardiac activity were noted. After killing of 15 head (5 percent), in whom upon clinical observation disruptions of cardiac activity had been noted, specific changes in the heart muscle were established (necrotic foci). Following development of the disease temporary disruptions of cardiac activity were noted in 9 head (3 percent) and permanent disruptions in 2 head (0.67 percent). According to our observations, such disruptions of cardiac activity in young cows are observed considerably more often (3 to 5 percent).

In literature on the subject there are indications that foot-and-mouth disease can cause symptoms of pharyngitis, bronchitis, bronchial pneumonia, emphysema, and others. This has been described by certain authors (Nocard and Leclainche) as a special "respiratory form of foot-and-mouth disease". Nevertheless, these are very rare cases, not typical of foot-and-mouth disease, and should be regarded, so it seems to us, as complications.

In malignant cases of foot-and-mouth disease in cattle the clinical picture of the sickness is but little characteristic. At first the sickness develops in typical form, but then, in the stage when recovery has already begun (5th to 7th day) there comes a sudden deterioration and death (50 - 60 percent). The most clearly evident symptoms: intense weakness and depression, shivering, quickened respiration, quickened pulse (up to 120 to 140 beats in adult cattle and up to 200 to 240 beats in calves), irregular (arhythmical) heart beats, and others. Death comes in consequence of paralysis of the

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heart, being able to come without any prodromal phenomena.

Dohlmuth observed several cases of foot-and-mouth disease accompanied by diarrhea and hematuria with fatal outcome. These phenomena were noted in the period when the animal had already begun to recover. Such a form of foot-and-mouth disease is observed mainly in cattle. The reasons for malignant foot-and-mouth disease have been given little study.

Depending on the place of penetration of the virus, the development of primary aphthae can begin either in the buccal cavity (with penetration of the virus through the digestive tract, and then secondary aphthae appear at other "favorite" places), or on the extremities, or on the teats of the udder (with penetration of the virus through the damaged skin, and in this case, upon generalization of the infection secondary aphthae appear in the buccal cavity). While primary aphthae develop only on the place of penetration and multiplication of the virus, secondary aphthae can appear in the buccal cavity and simultaneously or in a little time on the extremities and the teats of the udder, in consequence of generalization of the process. Preventing this generalization of the process by means of therapeutic intervention or any other precautionary measure is usually unsuccessful.

In individual cases, if the animal possesses incomplete (relative) immunity to foot-and-mouth disease, the sickness can run its course without generalization of the process, i.e. with appearance of only primary aphthae. At the place of penetration and multiplication of the virus, there are one to two (and very seldom more) aphthae,

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while there are many secondary aphthae (plural aphthae). Consequently, on the basis of the time and place of appearance and the number of aphthae it is possible to judge whether they are of primary or secondary origin, while on the basis of external form, size and shape it is impossible to distinguish primary from secondary aphthae. The thickness of the walls of the primary and secondary aphthae is non-uniform, which depends on the thickness of the epithelial layer at the place of development of these aphthae. They are filled at first with transparent, colorless or lemon-yellow liquid (exudate), which with the passage of time darkens and acquires a whitish-gray color.

Interesting data with respect to the localization of foot-and-mouth disease irritations in adult cattle can be found in Ozerov's article. (Ozerov, A. I., "The Problem of Foot-and-Mouth Disease", Vet. praktika, No 3, 1930.) In one herd of 50 head of cattle the author observed irritations of the buccal cavity in 35 percent, of the buccal cavity and extremities in 35 percent, of the buccal cavity and teats in 20 percent, and finally, of the buccal cavity, extremities, and teats in 10 percent. Irritations of the membrane of the buccal cavity (lips, tongue, and gums), and also of the extremities and teats, in Ozerov's opinion, are the most typical of foot-and-mouth disease. It is inherently obvious that these relations among individual local irritations, as adduced by the author, cannot be applied to all foot-and-mouth-disease epizootics, but in the given case they are sufficiently typical of foot-and-mouth disease.

The duration of the course of the sickness in cattle depends on very many factors, but in nonmalignant cases it extends no longer

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than 8 to 12 days and only in cases of severe complications can it extend for two to three weeks and longer.

THE CLINICAL PICTURE OF FOOT-AND-MOUTH DISEASE IN SWINE

In natural infection with foot-and-mouth disease the incubation period in swine lasts an average of 36 to 48 hours (Frohner and Zwick), 30 hours (Harms). In Lamman's experiments of long ago (1880-1882), in swine placed in a building with litter contaminated with foot-and-mouth-disease virus irritations of all 4 extremities were observed on the fourth day. In artificial infection of swine primary aphthae develop on the place of injection of the virus within the first 12 to 36 hours, following which they rupture, the infection generalizes, and the general symptom complex of the sickness develops (Waldmann and Trautwein, Skomorokhov, and others).

In swine foot-and-mouth disease runs its course with irritations mainly of the extremities (Figure 21), but similar irritations are observed frequently on the snout and the teats and, very seldom, are observed in the buccal cavity. The first stage of development of the sickness in swine, just as in other animals, can easily be overlooked.

Böhm observed sharply defined dark-red spots on the sole of the extremities of swine killed in the incipient stage of the sickness, which he connected with the development of the primary aphthous process. In 75 percent of all cases Böhm noted these changes on the forward part of the sole, around the cleft of the hoof, and also in the corium of the sole. He assumes that the foot-and-mouth-disease process in swine can develop within the shoe-part of the hoof.

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Only with rise in the body temperature are there symptoms typical of this disease. With the coming of generalization of the infection the temperature rises, the general condition becomes depressed, desire for feed decreases or stops entirely, and the sick animal reclines more. On the skin of the extremities in the region of the cleft of the hoof, the coronary band and the heels

Plate 1. Aphthae and erosions on the snout of a pig.

there first appear reddishness, swelling, and painfulness, and then in these same places aphthae develop; these advance upward at times along the rear surface of the extremity to the ankle joint, leaving erosions of dark-red color, which soon are covered with a viscous substance and rapidly dry up in the form of scabs of exudate, under which regeneration of the epithelium takes place in 7 to 14 days. In individual cases the erosions bleed strongly. With strong affliction of the extremities with foot-and-mouth disease (which is observed rather often) the shoe-part of the hoof at times falls off completely. A new hoof is formed in 2 to 4 months. Affliction of the extremities with foot-and-mouth disease is always accompanied by pronounced limping. Healing of the affliction and the very outcome of the process depend a great deal on the condition of the swine and the timely provision of veterinary aid.

Figure 21. Foot-and-mouth disease of swine -- irritation on the sole of the foot in the region of the coronary band and heels of the forward extremities (original).

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With irritation of the buccal cavity in swine (which happens very seldom) aphthae and erosions appear, usually in small number. They do not cause sharply pronounced phenomena of aphthous stomatitis, and characteristic salivation appears only with severe affliction. Irritation of the snout is observed rather often: aphthae, which sometimes attain the size of a walnut or larger, form on it. Subsequently these aphthae rupture, erosions cover them with brown-colored scabs and soon afterwards heal. Certain investigators have observed in swine cases of an atypical course of foot-and-mouth disease, when the epithelium scales off without preliminary formation of a vesicle.

Aphthous irritations occur very often on the teats, especially in nursing sows. According to Cserovi's observations, specific irritations in the form of aphthae and erosions appear in nursing sows principally on the skin of the belly around the teats. Moreover, aphthous irritations have been observed in some sows on the snout and extremities.

In sucking-pigs foot-and-mouth disease runs its course, as has been said, in anaphthous form, with phenomena of acute catarrh of the stomach and intestines, and is accompanied frequently by disorder of the cardiac activity (myocarditis). At this age up to 50 or 60 percent of sucking-pigs perish.

Orlov describes in the following manner the clinical picture of foot-and-mouth disease in sucking-pigs: they become depressed, flabby; their outer skin loses its natural sheen, and the pigs die on the 1st to 6th day following commencement of the disease.

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In individual pigs the author noted in addition a swelling of the soft parts of the hoofs, necrosis of the coronary band, falling off of the shoe-part of the hoof, and lameness. Ozerov observed principally an affliction of the hoofs in sucking-pigs, the disease ending for the majority of them in falling-off of the shoe-part of the hoof, which evidently was connected with poor condition of the pigs.

We have had occasion (1936) to observe an epizootic of foot-and-mouth disease among swine in one subsidiary farm, where in the nursing sows foot-and-mouth-disease irritations were localized almost exclusively on the skin of the belly and the teats. Sucking-pigs developed foot-and-mouth disease in anaphthous form with irritation of the extremities, not infrequently ending in complete falling-off of the shoe-part of the hoof. Several sucking-pigs which were diseased died from acute catarrh of the stomach-intestinal tract. Upon dissection of the deceased pigs changes in the heart muscle in the form of small scattered spots were observed in them.

Bergmann observed foot-and-mouth disease of swine in atypical form, without appearance of aphthae. In cases of mortality of animals with this form of the disease he found that their heart muscles were light gray, sometimes yellowish, with protruding bands and spots. Calves injected with material from the heart developed foot-and-mouth disease.

THE CLINICAL PICTURE OF FOOT-AND-MOUTH DISEASE IN SHEEP

In natural infection of sheep the incubation period can last from 24 hours to 6 days (Frönner and Zwick), and with experi-

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mental infection an average of 17 hours (Lumbaum).

Plate 2. Erosions on the site of ruptured aphthae on the extremity of a pig. (From the museum collection of the Leningrad Institute for Specialising Veterinary Physicians.)

In sheep the extremities are principally affected. On the skin in the region of the coronary band and the cleft of the hoof redness, swelling, and a sensitivity appear at first, followed by the development of aphthae. The latter soon rupture and leave erosions which are covered with serous or serous-purulent exudate and scabs, under which regeneration of the epithelium takes place. Irritation of the extremities, most often of the forward ones, is always accompanied by pronounced lameness.

Considerably more seldom aphthae appear in sheep in the buccal cavity, mainly on the toothless arc of the gum, the upper lip, and the inner surface of the cheeks. Aphthae in the buccal cavity are very small -- from the size of a corn kernel to that of a lentil, and seldom larger. At the very beginning of the disease the sick sheep refuses food, the cud stops, the temperature rises, and the general condition is depressed. During period of lactation the udder is very often affected. Lambs develop more severe cases of foot-and-mouth disease than adult sheep. In nursing lambs the anaphthous form is most often observed, with phenomena of gastroenteritis with a high percentile mortality.

Lumbaum infected sheep artificially for the purpose of study of the clinical picture of foot-and-mouth disease. In his

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experiments primary aphthae developed on the site of infection in 17 hours, the size of a corn kernel and of whitish-yellowish color. The aphthae had very thick epithelial walls, which soon ruptured and left in their place erosions with a reddish base and sharply defined edges. In 40 hours (infrequently in 24 to 36 hours) following infection there came a sudden rise in temperature. The raised temperature was maintained for 60 to 100 hours, and then fell back to normal, also suddenly. Secondary aphthae in the buccal cavity developed only following the rise in temperature, and upon appearance of them the temperature fell to normal.

Development of the disease by the extremities in artificial infection came in 48 - 60 hours following infection. Aphthae appeared on the skin of the heels, the coronary band, and in the region of the cleft of the hoof. Their development usually coincided with the moment of lowering of temperature. Neither salivation or any other phenomena which are observed in cattle, particularly with affliction of the buccal cavity, were observed in sheep by Lambourn. Recovery came very rapidly, and the whole process usually ended in the course of 10 days.

Curson, during a foot-and-mouth-disease epizootic in one flock, observed in young ewes (15 months of age and not yet covered) during the period of sickness the appearance of milk in the udder, which was easily stripped. Following recovery the milk disappeared, and the udder resumed its former shape and size. Curson ascribes this to the effect of the virus, which can be eliminated through the udder.

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THE CLINICAL PICTURE OF FOOT-AND-MOUTH DISEASE IN GOATS

The incubation period in goats can continue from 2 to 6 days (Fortner and Honecker). The clinical picture of foot-and-mouth disease in goats has been given detailed description by Honecker, and also by Pain, Stoss, and finally Kuest. At the beginning of the disease the animal refuses food, the cud stops, and phenomena of tympanites and constipation, and finally of sloughing of the hoof, reminiscent of the picture of osteomalacia, are observed. The general condition is depressed, the hide loses its sheen, then becomes somewhat coarser, the temperature rises to 41.5 degrees and remains for several days, and finally falls back to normal. Sick animals spend more time lying down and get up with difficulty. In 3 to 4 days, and often even in 5 to 10 days, the animals again begin to take food.

erosions

erosions

Figure 22. Erosions on the mucous membrane of a goat's tongue (after Honecker and Fortner).

Foot-and-mouth disease in goats afflicts the buccal cavity and the extremities (Figure 22). At the beginning of the disease the mucous membrane of the buccal cavity becomes pronouncedly hyperemic, irritated, painful, and covered with a viscous film with small vesicles. Aphthous irritations in the buccal cavity

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appear in 1 to 3 days following infection. In distinction to cattle, aphthae in goats are small, flat, and appear on the upper and lower jaws, on the hard palate, on the inner surface of the lips and cheeks, and on the tongue. However, the usual place for formation of aphthae is in the corners of the lips and the lower lip. In 24 to 48 hours these aphthae rupture, and in their place erosions of various size and shape remain.

The erosions are also of very small proportions (from the size of a corn kernel to that of a pea) and of irregular shape. At first the base of the erosion is red, and then it gradually blanches and is covered with a fibrinous film which has the appearance of coagulated albumin. The erosions heal rather slowly. Complete regeneration of the epithelium ends in the course of 7 to 21 days. Sick goats hold the mouth closed, grit their teeth, the characteristic salivation which is observed in cattle not occurring in goats; there is also no smacking of the lips. A small quantity of saliva collects only in the corners of the mouth. A foul odor issues from the mouth, and constipation or diarrhea develops, the feces being covered very often with a film or even colored with blood.

Apart from the buccal cavity, foot-and-mouth-disease irritations also occur on the extremities. According to Honecker, irritation of the extremities with the appearance of exanthema and typical aphthous irritations is observed in 50 percent of all goats which develop foot-and-mouth disease. Irritation of the extremities (coronary band, heels) is accompanied by lameness. The aphthae which have developed soon rupture, and erosions form in their place, becoming rapidly covered with a scab under which regeneration of the epithelium takes

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place. Healing comes very soon and usually without serious complications.

Irritation of the udder in goats takes place evidently very seldom (Honecker and Fortner, Kuest, Grosse, and others). Exanthema on the udder in foot-and-mouth disease has been observed only by Trapel, Fortner, and Grosse. Aphthous irritations have been observed by them on the teats.

In individual cases aphthae occur also on other places of the skin of the udder which are not covered by hair. Often mere small "defects" of the epithelium arise (without formation of aphthae), the size of a lentil, and soon heal. Irritations on the teats heal very rapidly and leave no traces. The secretion of milk decreases, and its composition is markedly altered.

Honecker and Fortner, and also Pahn and Stoss, found changes in the kidneys and bladder of goats which had died of foot-and-mouth disease. In their opinion, this indicates that with foot-and-mouth disease in goats the pathological process spreads also to the urinary system.

In nonmalignant cases of foot-and-mouth disease, if they are not complicated by other infections, the process ends in 10 - 14 days, and the animal recovers. Mortality from foot-and-mouth disease in goats is very small. In individual years, in a period of considerable epizootics foot-and-mouth disease sometimes causes a high percentile mortality. In Germany during the epizootic of 1919 - 1921 mortality of goats reached 20 to 30 percent and in individual instances even 100 percent (Fröhner and Zwick).

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THE CLINICAL PICTURE OF FOOT-AND-MOUTH DISEASE IN CAMELS

In experimental infection of camels the incubation period is 48 hours (Krasovskiy). For natural infection of camels with foot-and-mouth disease a more or less detailed clinical picture has been described by Kobets on the basis of his observations in Central Asia in 1926.

On the first day he noted in a sick camel a general depressed condition; the animal lay down, refused food, and there was absolutely no cud. The mucous membrane of the mouth, gums, and lips was hyperemic. The temperature in the morning was 39.7 degrees and toward evening, when all phenomena of a severe case of disease had appeared, rose to 40.2 degrees.

On the second day the temperature was 40.1 degrees. On the inner surface of the lips, gums, and on the tip of the tongue vesicles (small aphthae) with a yellowish content appeared. The vesicles on the lips had an irregular shape and attained the size of a kidney-bean, but on the gums they were considerably smaller. The camel kept his mouth tightly closed at all times, and often produced the characteristic sound of smacking of the lips. At the same time conjunctivitis, swelling of the eyelids, and a purulent effusion from the eyes were observed. In addition, an effusion of slimy character from the nasal cavity was noted. Slight lameness appeared. The camel moved with difficulty and stepped cautiously. The animal lay down and refused feeding; there was no cud.

On the third day in the morning the temperature was 39.4

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degrees. The contents of the vesicles had become muddy, part of them having already ruptured, with erosions forming in their place. A slight salivation appeared, in the form of viscous, trailing, lengthy threads. In the evening the temperature had declined to 38.6 degrees.

On the fourth day the temperature in the morning was 37.7 degrees; the erosions had healed; the camel took food, began to move about, and the cud reappeared. The sickness lasted on the whole 5 to 6 days and ended with recovery. In another case, so Kobets reports, disease of a camel ended in a fatal outcome. He likewise observed a case of infection of a young camel by a female, the young camel dying with symptoms of acute gastroenteritis.

The first clinical picture of foot-and-mouth disease in camels was evidently described by Kovalevskiy in 1913. According to his description, it is reminiscent of the clinical picture for cattle: the appearance of primary aphthae, increase in temperature, salivation, deterioration of the general conditions, and finally, irritation of the extremities.

Krasovskiy described the picture of foot-and-mouth disease in camels exposed to experimental infection. On the second to third day following infection a general weakness is noted, which on subsequent days gives way to a pronounced depressed condition. Increased temperature, loss of appetite, and pronounced loss of weight are observed (Figure 23). In the buccal cavity on the mucous membrane of the lips and on the tongue aphthae of oblong-oval shape, the size of a nut, appear in 48 hours after infection. There is no

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Figure 23. Foot-and-mouth disease of camels (original). Development of foot-and-mouth disease causes acute loss of weight; the camel at right has developed foot-and-mouth disease.

salivation. In 72 to 76 hours aphthae appear on the extremities; an edema of the extremities is observed, spreading from the sole to the carpal section, and passing into phlegmon.

Healing of the aphthae and amelioration of the general condition begins after the 5th to 7th day.

As may be seen from the descriptions, the course of foot-and-mouth disease in camels is actually reminiscent of the picture of foot-and-mouth disease in cattle.

THE CLINICAL PICTURE OF FOOT-AND-MOUTH DISEASE IN REINDEER

In experimental infection the incubation period for reindeer is 25 to 30 hours (Magnusson).

In northern reindeer foot-and-mouth disease runs its course with the same clinical symptoms as in cattle. According to Ekkert (1898), "in reindeer which have developed foot-and-mouth disease vesicles appear on the membrane of the tongue and gums; these vesicles are filled with a light fluid and subsequently burst; the afflicted parts are little by little denuded of the membrane covering them. Soon the process of sickness spreads to the hoof and causes loss of the shoe-part of the hoof. Recovery in such cases comes very slowly, and some sick animals must be killed. Separation of

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the shoe-part of the hoof in the region of the hoof as well as the upper pair of hoooflets is preceded by formation of foot-and-mouth-disease vesicles in the cleft of the hoof and by subsequent purulence."

Ekkert and Devel' (1900), in experimental infection with foot-and-mouth disease of reindeer, describe the clinical picture of the sickness in the following manner. On the third day following infection a rise in temperature comes, hyperemia of the mucous membrane in the buccal cavity is noted, and small aphthae, very pronounced on the fourth day, gradually develop. The aphthae occur in scattered form on the tongue and gums. On the fifth day they rupture, and in their place erosions remain. Salivation appears. The erosions are soon covered by a clotted film under which regeneration of the epithelium takes place. The rise in temperature often lasts to the 5th or 8th day. Complete recovery comes on the 11th day after the beginning of the disease.

Magnusson observed, in experimental infection of reindeer, that in 36 hours following infection an aphtha appears on the site of the injection, and in 48 hours the temperature rises to 40.1 degrees, and on the fifth day reaches 40.6 degrees. In 18 days foot-and-mouth-disease irritations were observed in the region of the coronary band of the hoofs. The sickness ended in recovery. In another young reindeer the temperature rose (to 40.3 degrees) four days after infection and there were aphthae on the tongue and coronary band of the hoofs.

THE CLINICAL PICTURE OF FOOT-AND-MOUTH DISEASE IN GUINEA PIGS

The incubation period in guinea pigs, with artificial infection

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in the plantar surface of a rear extremity, lasts 12 to 96 hours (Waldmann and Pape). Upon infection of guinea pigs with virus which has first been propagated in a guinea pig, the incubation period usually is 12 to 48 hours and seldom longer, but with infection with virus from cattle can extend to 4 or 8 days. In extremely infrequent cases the incubation period, according to our observations, lasts up to 9 days. A primary aphtha develops on the site of injection of the virus in the course of 12 to 24 hours, following which generalization of the infection comes. The appearance of a primary aphtha is preceded by an inflammatory reaction on the site of injection of the virus, in the form of reddishness, swelling of the extremity, pain, and other symptoms. With the coming of generalization of the infection secondary, plural aphthae appear in the buccal cavity and on all the remaining three extremities (the guinea pig is usually infected via one of the rear extremities).

In guinea pigs the aphthae on the extremities do not rupture (as in other animals), and following maturity gradually decrease in expanse and dry up, and the dead epithelium crumbles away. The stage of erosions seemingly is omitted in this case. In the buccal cavity aphthae and erosions are observed. Intensified in virulence by passages, the virus very often causes heavy mortality in guinea pigs.

COMPLICATIONS IN FOOT-AND-MOUTH DISEASE

Among the most frequently observed complications it is essential to mention various disorders of the heart activity (pulsations, weak, accelerated, or arythmic pulse, myocarditis);

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miscarriages in pregnant animals, particularly in the latter stages of pregnancy; mastitis (parenchymatous inflammation of the udder, abscesses of the udder, atrophy); abscesses and necroses of the skin; septic processes; arthritis; necrosis of the bones; loss of the shoe-part of the hoof; pharyngitis and emphysema; conjunctivitis; nervous symptoms; convulsions; paralysis; and secondary infections.

In affliction of the extremities the foot-and-mouth-disease process can be complicated by various secondary infections, in which case sickness can be considerably protracted. Such complications are usually accompanied by painful lameness and require prolonged treatment.

In affliction of the udder due to foot-and-mouth disease complications are possible in the form of parenchymatous inflammation or even of abscesses in one or all four parts of the lactary gland. These complications also require persistent and prolonged treatment. From the point of view of spreading of the infection sick animals with such infections do not represent danger for other animals, and in removal of quarantines from contaminated farms should not be considered as animals diseased with foot-and-mouth disease.

Certain investigators are inclined to ascribe to foot-and-mouth disease the property of opening the "gates" for other infections, particularly for the Siberian ulcer. However, the greater frequency of cases of Siberian ulcer observed at times during foot-and-mouth-disease epidemics depends more on the weakening of the natural resistance of sick animals' organisms than on easier

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penetration of the infection through erosions in the mucous membrane (Hutyra and Marek).

In certain weaker cows which have developed foot-and-mouth disease in the final period of pregnancy, the length of the latter was shortened to 280 - 272 days, i.e. calving took place 5 to 13 days early (Ozerov).

With reasonable care and good condition on the part of the animals, and also with timely therapeutic intervention many of these complications may be prevented.

ATYPICAL AND ABORTIVE FORMS OF FOOT-AND-MOUTH DISEASE

Many authors have repeatedly described the so-called atypical forms of foot-and-mouth disease. (An atypical form of foot-and-mouth disease in adult cattle was described by the Russian investigators Ravich (1873) and Shadrin (1891), earlier than by many other, foreign authors.) Into the category of atypical forms of foot-and-mouth disease fit those cases of foot-and-mouth-disease infection where the infection runs its course in the absence of the most characteristic, or in other words, typical clinical symptoms of the disease. Sometimes the concept of atypical foot-and-mouth-disease infection is applied by certain authors to a whole epizootic, these authors referring to an atypical foot-and-mouth-disease epizootic. Atypical forms of foot-and-mouth disease are most often encountered among cattle.

Bewan in Southern Rhodesia and Welton in southern China observed among cattle epizootics of foot-and-mouth disease which ran their course with extremely weakly pronounced symptoms of the disease,

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and the disease itself spread very slowly. They described these epizootics as atypical.

In Bewan's opinion, the causes of atypical foot-and-mouth-disease epizootics stem exclusively from "local conditions", by which he means comparative resistance to foot-and-mouth disease of local indigenous cattle, living and climatic conditions, and others. This does not depend, in Bewan's words, on the biological peculiarities of the foot-and-mouth-disease virus, since upon being tested in another locality the latter has caused typical development of the clinical picture of foot-and-mouth disease in cattle, and is in no way distinguished by its virulence from other strains of foot-and-mouth-disease virus.

In addition to atypical forms, abortive forms of foot-and-mouth disease are also encountered in conditions of natural development of foot-and-mouth-disease epizootics.

Related to the category of these forms are cases where the incipient disease suddenly stops ("breaks off") and rapid recovery of the animal comes. Cases are possible, finally, of foot-and-mouth disease in the form of "attenuated" (symptomless) types, where the animal develops the disease in complete absence of typical symptoms of sickness and rapidly recovers.

MALIGNANT FOOT-AND-MOUTH DISEASE

In foreign countries a malignant type of foot-and-mouth-disease epidemic has been noted repeatedly, accompanied by heavy mortality among diseased animals. In Germany during the foot-and-mouth-disease

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epizootic of 1920-21 the mortality in individual localities reached 80 to 100 percent. During the panzootic of foot-and-mouth disease in 1937-39, which attacked the entire European continent (Italy, France, Germany, Switzerland, and others) right up to the shores of the Baltic Sea, certain countries lost an enormous quantity of stock in consequence of the malignant form of the disease.

In prerevolutionary Russia malignant foot-and-mouth disease sometimes brought very heavy losses to animal husbandry. In 1915 the mortality of cattle in certain localities reached 50 percent, and in one of the farms with Brown Swiss stock about 80 percent of the whole herd died following artificial infection.

In 1905, 77 gubernias and oblasts were attacked by foot-and-mouth disease, mortality among cattle being 35.3 percent and for sheep 4.25 percent. In 1882 in Tver gubernia the mortality of cattle from foot-and-mouth disease was 41 percent, for Tobol'sk gubernia 38.4 percent, and for Tomsk gubernia 42 percent.

In the past there were many such examples of malignant foot-and-mouth disease.

The malignant form of foot-and-mouth disease should not be associated with individual cases of severe (complicated) types of infection. In this case mortality of individual animals is also possible, but not from foot-and-mouth disease -- it is due to various complications. Malignant foot-and-mouth-disease epizootics are always accompanied by massive mortality of animals, it being somewhat distinguished from the nonmalignant form of the disease by the character of development of the infection itself as well as the

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pathologo-anatomical picture of the disease.

The malignant form of foot-and-mouth disease is encountered among cattle as well as other types of animals. Among cattle it has long been known. A malignant form of foot-and-mouth disease among reindeer was observed by Grüner, among goats by Honecker, and in guinea pigs by Gins and Fortner.

We have seen cases of a malignant form of foot-and-mouth disease in guinea pigs, during which mortality reached 80 percent.

The essence and cause of malignant foot-and-mouth disease remain unexplained up to the present. Vyshelesskiy sees the cause of malignant foot-and-mouth disease "in the extremely virulent infectious basis of foot-and-mouth disease". Waldmann assumes that the reason for malignant foot-and-mouth-disease epizootics may be an intensification of the virulence of the virus in consequence of passage of it in various types of animals susceptible to foot-and-mouth disease. Under laboratory conditions it can be achieved by repeated passage of the virus in various types of animals susceptible to foot-and-mouth disease.

Ernst, Wimman, and Miller hold that the cause of the outbreak of a malignant epizootic of foot-and-mouth disease in Germany in 1920-1921 was restoration of the composition of herds following the Imperialist War. In Terni's opinion, in localities where milk cattle are kept restoration of the composition of herds over definite intervals of time (5 to 6 years) can facilitate the intensification of the virulence of the virus.

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Certain investigators assume the possibility of appearance of virus with especially high virulence in years of malignant epizootics. Waldmann has repeatedly taken a stand against such a point of view.

It is possible, finally, that the occurrence of malignant forms of foot-and-mouth disease is connected with the influence of other factors which are not always subject to being taken into account. It is also typical that foot-and-mouth disease usually runs its course in nonmalignant form at the beginning of an epizootic, and then under the influence of some causes unknown to us takes a malignant course. Such a transition from the nonmalignant form to the malignant, according to Wimman's data, can be accomplished over the duration of the whole period of development of the epizootic, but in individual herds both forms of foot-and-mouth disease may be observed at the same time.

With malignant foot-and-mouth disease, clinical appearances are the same in the early stages of development of sickness as with nonmalignant cases. On the 4th to the 7th day following the first signs of sickness, i.e. in the stage when recovery has already begun, an abrupt deterioration suddenly takes place. A general pronounced weakness, accelerated pulse with irregular heartbeats, and muscular trembling appear; the animal refuses food, the cud stops, the gait becomes unsteady, and in a short time the animal dies.

Following death of the animal from malignant foot-and-mouth disease the most characteristic pathologo-anatomical changes are found in the cardiac musculature, in the parenchyma itself as well

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as in the interstices.

In malignant cases of foot-and-mouth disease certain authors (Wester and others) have observed symptoms of paresis -- paralysis of the hind quarters very reminiscent of puerperal paresis. We observed (1937) a similar disease on one of the suburban farms. During the period of recovery of the animals a tremendous sickness began suddenly, typical of malignant foot-and-mouth disease. In many cows, besides, symptoms of paresis were noted. Pathologo-anatomical dissection of several head of these animals which had died, performed for diagnostic purposes, did not give, however, a characteristic picture for foot-and-mouth disease of malignant type. In his day Terni described a special nervous form of malignant foot-and-mouth disease in cattle, which has already been referred to above. In this respect further observations and confirmation of these data under experimental conditions are necessary.

CHANGE IN THE COMPOSITION OF BLOOD IN FOOT-AND-MOUTH DISEASE

This question has not yet received adequate scientific clarification. There are only several works in all, mainly by Soviet investigators, which are dedicated to the question of changes in the morphological composition of blood, and the question of variations in the inorganic elements of the blood remains almost entirely untouched.

Knoblauch, on the basis of hematological investigations, reached the conclusion that at the beginning of the disease eosinophilia and lymphocytosis occur. Orlov established that in sick animals the quantity of lymphocytes and eosinophils increases, and the quantity

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of neutrophils, on the other hand, decreases.

Dorofeyev, Skomorokhov, and Kudryavtsev studied changes in the quantitative composition of the blood of cattle in connection with the development of the clinical picture of foot-and-mouth disease. On the basis of their investigations they established that before the advent of the moment of temperature rise to the maximum, and consequently before the development of clinical symptoms, the absolute quantity of white and red corpuscles increases markedly, and with increase in the temperature falls below normal with the appearance of clinical symptoms. In the beginning of the disease neutrophilia with a small movement to the left is observed, and then lymphocytosis. The percentage of monocytes increases from the moment of infection until the beginning of recovery, and then decreases to normal.

This same question has been studied in more detail by Dorofeyev, who established that changes in the morphological composition of blood begin even before the temperature rises and, in any case, before the appearance of clinical symptoms. At the beginning of sickness neutrophilia (with a small shift to the left), monocytosis, and then lymphocytosis are observed. With the temperature's fall and the development of clinical symptoms the absolute number of erythrocytes and monocytes again becomes normal.

Zhuraleva studied the change in the morphological composition of the blood in foot-and-mouth disease in cattle, swine, and guinea pigs, and reached the following conclusion: with the development of clinical symptoms (rise in temperature and appearance of primary

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aphthae) the absolute quantity of leucocytes increases considerably. With decrease in temperature and subsiding of clinical symptoms of the disease, the absolute number of leucocytes falls to normal, and in some instances even below normal. At the beginning of sickness neutrophilia is observed, which in swine produces a small movement to the left toward the tubercular nuclei, and then is replaced by lymphocytosis. The quantity of monocytes at the beginning of sickness remains normal, but increases with the development of the disease, and toward the moment of recovery comes back to normal. The quantity of eosinophils falls below normal in the first phase of the disease, or disappears completely, and toward the moment of recovery comes back to normal. The absolute quantity of erythrocytes remained unchanged in all experimental animals.

Khokhlachev, studying the aspect of the blood, observed in experimental foot-and-mouth disease that with the rise in temperature an increase in the absolute number of leucocytes is noted, but the quantity of erythrocytes and the hemoglobin content, on the other hand, decrease.

Revo studied changes in the composition of the blood in guinea pigs and established that development of the disease by guinea pigs is accompanied by neutrophilia and lymphopenia in the white blood and by polychromasia, anisotocytosis, poikilocytosis, and the appearance of erythro- and megablasts in the red blood.

The question of variations in the inorganic elements of the blood was first studied by Skomorokhov, Dorofeyev, and Kudryavtsev, and it was established that the irregular variations of the quantity of Ca, and also changes in electrical conductivity and pH of the blood, are almost parallel, attaining a minimum value at the moment

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of the animal's severest condition. The question of variations in the inorganic elements of the blood of animals in foot-and-mouth disease is in need of further study.

CHANGES IN THE COMPOSITION OF MILK

The composition of the milk of sick animals changes sharply, quantitatively as well as qualitatively. Andrewes could not prove the presence of virus in two test tubes of blood taken during the incubation period. The virus appeared only in four hours following the rise in temperature. Brandt proved experimentally that all these changes with respect to the secretion and composition of milk occur even before the appearance of clinical symptoms of disease. These changes are most strongly pronounced in severe cases of disease and, on the other hand, can be insignificant with mild cases. On dairy farms, particularly during the period of maximum lactation, the drop in milk production during sickness of the stock at times reaches 30 - 40 percent of the overall amount. With individual milk cows the milk yield is not restored over a long period, even after recovery, at times not until the next calving.

Qualitative changes in milk occur mainly with respect to fat, albumins, acidity, milk sugar, and volatile fatty acids. The fat content either drops abruptly (to 1.2 percent) as observed by Rievel, Ernst, and others, or, on the other hand, rises sharply (to 11.5 percent), as in Kreis' experiments. The refraction index of the fat, in connection with the increase in the content of the latter, also increases (Karklin). However, usually a decrease in the

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fat content of milk is observed. The more severe the case of disease, the more strongly pronounced are these variations.

In the milk of cows which have developed foot-and-mouth disease the casein content, as established by the experiments of Winkler, and also of Brandt, is always lower than before sickness. The acidity of the milk decreases considerably, in consequence of which the pH increases (Schwarz, Mesger, Fesser, and Gepp).

Certain authors, on the other hand, have even observed an increase in acidity (Martin). The reaction can be either acidic or alkaline. The general content of albumins in milk is either lower than normal, or stays in the normal range.

The amount of casein decreases (Daum, Grimmer, Rievel, Karklin, and others), and the quantity of albumin and globulin, on the other hand, increases (Karklin and others). Many authors note a tendency toward curdling on the part of milk, in consequence of its increased globulin content (Martin, Rievel, Mesger, Fesser, and Gepp).

The content of milk-sugar usually decreases, but in the period of the disease's most advanced stage it can increase (Schwarz).

The quantity of volatile fatty acids decreases sharply at the beginning of the disease (Karklin and others), and toward the moment of recovery is restored. Its reaction with peroxidases is vigorously positive. The increment in catalases is inconsiderable (Schwarz).

The solid content can vary greatly, reaching 11.01 - 27.20 percent (Honigmund, Zaribnitzky). Different manifestations in

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connection with the study of the milk of sick animals must be laid to their individual peculiarities as well as to the specific character of the infection itself, which causes substantial deviations in the pathology of the foot-and-mouth-disease process in one and the same type of animal.

Upon development of foot-and-mouth disease by animals special attention must be given to increased feeding.

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CHAPTER VI

THE DIAGNOSIS OF FOOT-AND-MOUTH DISEASE

CLINICAL DIAGNOSIS

Timely and accurate diagnosis of foot-and-mouth disease are of decisive importance for its rapid localization and liquidation within the confines of the primary center of contamination. As a rule, clinical symptoms in sick animals are well pronounced and are characterized by great constancy with respect to their localization in the sick animal's system. In addition, foot-and-mouth disease is typified by the severe course of the infection and the epizootic spread of the disease. Therefore, the diagnosis of foot-and-mouth disease may be based on clinical-epizootiological data, without recourse in this instance to any supplemental methods of diagnostic investigation.

Difficulties in the performance of a diagnosis may arise only with mediocre cases of infection when typical clinical symptoms of the disease are lacking. Atypical forms of foot-and-mouth disease are encountered rather infrequently.

With the development of foot-and-mouth disease by cattle, diagnosis may be based on specific irritations in the buccal cavity in the form of aphthae and erosions on the mucous membrane of the upper and lower lips, the tongue, the gums, the hard palate, and at times the skin of the front of the nose and around the nasal orifices. Irritation of the buccal cavity is accompanied by abundant

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Difficulties in the performance of a diagnosis may arise only with mild cases of infection when typical clinical symptoms of the disease are lacking. Atypical forms of foot-and-mouth disease are encountered rather infrequently.

With the development of foot-and-mouth disease by cattle, diagnosis may be based on specific irritations in the buccal cavity in the form of aphthae and erosions on the mucous membrane of the upper and lower lips, the tongue, the gums, the hard palate, and at times the skin of the front of the nose and around the nasal orifices. Irritation of the buccal cavity is accompanied by abundant

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salivation and the "smacking of the lips" - typical of foot-and-mouth disease. Simultaneously, or somewhat later, foot-and-mouth disease afflictions -- aphthae and erosions -- may be observed on the extremities and udder too. Affliction of the extremities is usually accompanied by painful lameness. High temperature (40.5-41.5 degrees) is observed only during the period of generalization of the infection; with the appearance of secondary (plural) aphthae it again drops to normal. All remaining symptoms of the disease -- a depressed condition, refusal of food, decline in the secretion of milk, rapidly advancing loss of weight -- only supplement the specific clinical picture of the disease.

In calves of very young age, foot-and-mouth disease often runs its course in anaphthous form with the appearance of acute enterocolitis, which frequently ends in lethal outcome of the disease. Diagnosis in such cases can be based on compound data -- clinical conditions and pathologo-anatomical changes. The presence of cases of foot-and-mouth disease sickness among adult cattle is an additional indication which can lead to basing the diagnosis on foot-and-mouth disease. In swine the diagnosis of foot-and-mouth disease is based ordinarily on the observation of aphthous irritations on the extremities, snout, or udder (particularly in sows with litters). In the buccal cavity aphthous irritations very seldom occur. Foot-and-mouth disease spreads to the entire group of animals with unusual rapidity. Widespread lameness is observed. In individual animals high temperature, trembling, and depressed condition are noted. In sucking-pigs foot-and-mouth disease runs its course in anaphthous form and usually ends lethally.

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In sheep, mainly the extremities are affected, causing extensive lameness. Aphthae and erosions form in the region of the coronary band, the heels, and the cleft of the hoof. The foot-and-mouth disease process is frequently complicated by secondary infections. In the buccal cavity aphthous irritations may likewise be observed; although not always. Salivation is usually not present in such cases. Diagnosis of foot-and-mouth disease in sheep can be based only on consideration of epizoological data.

Development of foot-and-mouth disease on the farm usually begins with cattle, but in the presence of other animals susceptible to the disease it spreads rapidly to all remaining types of animals, if the affected herd has not been submitted to timely and most riporous isolation. However, it must be remembered that in practice individual outbreaks of foot-and-mouth disease are known where the disease attacked only cattle and did not spread to other types of animals. Cases are also known where only a few pigs contracted foot-and-mouth disease on a farm.

DIFFERENTIAL DIAGNOSIS

In cattle, foot-and-mouth disease may be confused with infectious vesicular stomatitis. The latter runs its course in much the same manner as foot-and-mouth disease, with affliction of the membrane of the buccal cavity. At times, together with local irritation of the buccal cavity, there is simultaneous observation of various changes on the extremities caused by other factors. Cotton recommends, for differential diagnosis in such cases, infection of

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a horse which is susceptible to vesicular stomatitis and not to foot-and-mouth disease. Infection should be made in the membrane of the tongue. Swine and guinea pigs are not useful for differential diagnosis in such cases since both diseases cause the same symptoms in inoculated animals.

Incidentally, Cotton points out that although changes during vesicular stomatitis in cattle and guinea pigs are very similar to the same changes during foot-and-mouth disease, these diseases are nevertheless distinguished from each other by degree of infectivity, course, and character of the clinical picture itself. Vesicular stomatitis usually runs its course without a rise in temperature (Zwick).

Foot-and-mouth disease can sometimes be confused with mycotic stomatitis, which is caused by various fungi (molds, etc.), and also with aphthous and pustular dermatitis. But these diseases run their course without formation of vesicles, inflammation of the mucous membrane having a diffuse, spread-out character.

Ostertag and Bugge have observed a "papular" stomatitis in cattle, which likewise ran its course without formation of vesicles and rise in temperature. It is sometimes possible to take this disease for the atypical form of foot-and-mouth disease, which is encountered, however, very seldom. Kantorovich described an infectious exanthema in cattle with irritation of the membrane of the buccal cavity, udder, and extremities. Only cattle proved susceptible to this disease (Zwick).

Tsion and Rayevskiy have recently described a grippe in cattle

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which in its clinical picture is somewhat reminiscent of foot-and-mouth disease. With this disease a transparent, non-viscous, foamy saliva is exuded from the buccal cavity with defects in the mucous membrane usually lacking. From the nasal cavity a semitransparent serous liquid is exuded; at times drying on the flanges of the nose in the form of elastic crusts. In addition, an abundant flow of tears is observed on both sides.

In contrast to foot-and-mouth disease, the grippe affects cattle only and does not spread to other types of cloven-footed animals, even in close contact. The aphthous irritations on the mucous membrane of the buccal cavity, typical for foot-and-mouth disease, and also affliction of the extremities (in the region of the coronary band and heels) are invariably lacking with grippe. The young (calves) are more resistant to grippe than adult stock, seldom become sick, and then without complications and mortality.

Suspicion of foot-and-mouth disease in cattle can arise with actinomycotic irritation of the tongue. The latter almost always has a sharply limited character: afflicted are the dorsal surface of the tongue in front of the cylinder-shaped thickness and the taste buds (papillae fungiformes). With foot-and-mouth disease these taste buds are not affected. Actinomycosis is usually observed in the form of sporadic cases and never assumes the character of an epizootic.

Traumatic damage to the mucous membrane of the buccal cavity, in the form of various defects and erosions, particularly at the base of the tongue, on the inner surface of the lips, various burns and irritations, potato-leaf poisonings, etc., can also sometimes

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cause suspicion of foot-and-mouth disease, but all these injuries involve little that is typical of foot-and-mouth disease.

With irritation of the hoofs, foot-and-mouth disease can be confused with an inflammation of the cleft of the hoof and the coronary band which is caused by traumatic factors (panaritium). With foot-and-mouth-disease irritation of the hoofs, diagnosis can be made with little difficulty when such irritation has been preceded by irritation of the buccal cavity or in the presence of other epizoological data.

Foot-and-mouth-disease irritation of the udder in cows, in the absence of other clinical symptoms and epizoological data typical of this disease, can be confused with cow-pox; however, with cow-pox the vesicles are smaller in size than foot-and-mouth-disease vesicles; do not merge together; and, in addition, at the vesiculosum stage a small hollow ("navel") forms at their center. Foot-and-mouth disease aphthae usually develop in the form of pronounced vesicles, often run together, and in such manner form aphthae of large proportions and irregular shape. With foot-and-mouth disease the aphthae (for all animals except the guinea pig) invariably rupture, leaving around the edges scraps of epithelium. In cattle with cow-pox only the udder is affected, while with foot-and-mouth disease irritations are observed simultaneously in the buccal cavity, on the extremities, and in other places.

In swine with affliction of the hoofs foot-and-mouth disease can be confused with traumatic damage. Such damage may take place during transportation, especially in winter (freezing). It some-

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times resembles foot-and-mouth-disease erosions, but the aphthae typical of foot-and-mouth disease are always in absence. With irritation of the mucous membrane of the buccal cavity, foot-and-mouth disease can be confused with stomatitis caused by various factors (scorbutus, epizootic pneumonia, etc.). However, all these irritations occur without preliminary formation of aphthae. In scorbutus, moreover, bleeding, erosions, and ulcers are observed mainly on the gums. Finally, foot-and-mouth disease in swine with irritations of the mucous membrane of the buccal cavity is generally very seldom observed.

Figure 3. Foot-and-mouth-disease irritation of the tongue of cattle. Erosions in the stage of healing. (From the museum collection of the Leningrad Institute for the Improvement of Veterinary Doctors).

With irritation of the skin of the udder foot-and-mouth disease can be confused with cow-pox, particularly with the atypical form of cow-pox which has been described in the USSR by Boyarshinov and Likhachev.

In the USA a disease unknown in other countries is observed among swine -- the so-called "vesicular exanthema of swine", -- which runs its course in the form of a vesicular rash. From its clinical picture this disease is strongly reminiscent of foot-and-mouth disease and cow-pox. The horse has little susceptibility to vesicular exanthema of swine and is infected only with great difficulty. In vesicular exanthema of swine the specific inclusions --

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Paschen's bodies -- typical of cow-pox are absent in smears prepared from the contents of vesicles. Vesicular exanthema among swine usually runs its course in the form of an epizootic. In the USSR this disease has so far been recorded by no one. Differentiation of foot-and-mouth disease from cow-pox and vesicular exanthema is also possible on the basis of the characteristic development of aphthae in foot-and-mouth disease and their localization in "favorite" places.

In sheep and goats, ulcers of necrobacillotic origin are sometimes observed on the mucous membrane of the buccal cavity, especially on the tongue. These ulcers are very suggestive of the picture of foot-and-mouth disease in the stage of healing of the erosions in the buccal cavity. Irritations of the same origin are observed, at the same time, on the extremities, too, which causes even greater suspicion of foot-and-mouth disease if, in addition, there are known epizoological premises for such suspicion. Exclusion of foot-and-mouth disease in this case is possible only by means of mass clinical inspection of sheep and goats and analysis of epizoological data.

In mass clinical examination of sheep it is not possible in a single instance to observe on the mucous membrane of the buccal cavity the aphthae which are typical of foot-and-mouth disease or fresh erosions with scraps of epithelium along the edges at the site of ruptured vesicles. The presence of necrobacillosis can be verified by means of bacteriological research. Foot-and-mouth disease can also be excluded or verified by means of bio-tests (swine of all ages are susceptible to foot-and-mouth disease, while

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mainly sucking-pigs and young pigs under 4 months old develop necrobacillotosis).

In sheep and goats with irritation of the extremities, foot-and-mouth disease can be confused with various traumatic injuries in the region of the cleft of the hoof, the heels, and the coronary band. With foot-and-mouth disease these irritations are usually observed on the forward part of the cleft of the hoof. At first a vesicle develops, containing the virus in the form of "lymph", and then it ruptures and an erosion appears in its place. In sheep and goats cases of stomatitis are sometimes observed which are caused by various factors, but they are always of diffuse character and, most important, the aphthae and erosions typical of foot-and-mouth disease are not present on the mucous membrane.

Magnusson observed a unique rash on the mucous membrane of goats' tongues which suggested herpes, it being possible to confuse the latter in the stage of healing, with foot-and-mouth disease. These changes, according to Magnusson's observations, affected only the upper layer of epithelium, i.e. the Stratum corneum. Evidently this disease in goats is very seldom encountered and has so far not been described by other authors in literature in the field.

In reindeer, foot-and-mouth disease can be confused with necrobacillosis ("hooflet"). Foot-and-mouth disease runs its course in reindeer, just as in other animals, in acute form with irritation of the mucous membrane of the buccal cavity and extremities, assuming the character of an epizootic. Mortality of reindeer with foot-and-mouth disease is connected mainly with com-

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plications of all types due to septic processes on the extremities caused by various secondary infections. With atypical forms of foot-and-mouth disease, and also with malignant cases, conclusive diagnosis of foot-and-mouth disease can be based on clinical and pathologo-anatomical data, the character of the disease, the spread of infection, and finally, injection of material from affected tissues or organs into experimental animals (cattle, swine, guinea pigs).

SEROLOGICAL REACTIONS

Serological reactions as a method for the diagnosis of foot-and-mouth disease do not have great practical significance, inasmuch as there are adequate clinical-epizootological data in typical cases of foot-and-mouth disease for making a diagnosis. However, serological reactions as a method of laboratory research on foot-and-mouth disease can be very useful for the study of questions of immunity and immunization.

Preparation of specific type-antigens can also be used for the differentiation of types of the foot-and-mouth-disease virus.

Study of serological reactions in foot-and-mouth disease has engaged very many investigators (Lourens, 1909; Favero, 1914; Ernst and Mensen, 1922; Waldmann and Trautwein, 1923; Misinescu, Baroni, and Kalinescu, 1923; Urbani, 1927; Zachelaria, Boquet, and Urbani, 1923; Minett, 1927; Olitsky, Traum, and Schoening, 1928; Titze, 1928; Ciuka, 1929; Flaum, Sakvarelidze, 1933; Solov'yev and Helm, 1933; Galea, 1935; Frenkel, 1937; and others), but many of them have obtained negative results.

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Greatest interest is embodied in the scientific findings in this field which have been produced by French and Soviet investigators. Ciuka was one of the first to obtain positive results with foot-and-mouth-disease antigens which he had prepared in a complement-fixation reaction. For preparation of the antigen Ciuka used virus in the form of aphthous lymph or in the form of epithelium of aphthae of the guinea pig, collected by him 18 to 24 hours following infection. In the latter case, epithelium obtained from the guinea pig was first cut into fine pieces and then ground up in a porcelain mortar with a small amount of sand (for better grinding). To the resultant "emulsion" a physiological solution of sodium chloride was added in proportion of 1:10. Following this, the prepared emulsion was left for 8-10 hours; first at room temperature with frequent shaking-up, and then was place in a refrigerator. In 15 to 60 days the contents were filtered, first through a paper filter, and then through an asbestos Seitz plate. The filtrate thus obtained remained still virulent for 3 to 6 months of storage in refrigeration.

For setting-up complement-fixation reactions, Ciuka used inactivated serum and complement of guinea pigs. It turned out that convalescent guinea pigs, beginning as early as the 7th day after infection, provide a rather pronounced hemolysis preventive which reaches its maximum toward the third week. In two months following infection, it begins gradually to disappear, and in 72 days the prevention of hemolysis is completely halted. As a result of their experiments with the performance of the complement-fixation reaction for foot-and-mouth disease, Trautwein and Reppin, and also Flaum, did not confirm the data obtained by Ciuka.

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Sakvarelidze prepared foot-and-mouth-disease antigen by means of extraction of the antigenic substance from epithelial cells containing the virus, which in the complement-fixation reaction gave positive results. For this purpose he exposed the epithelium of aphthae to deep-seated destruction, and then extracted the antigen with alcohol (95 percent alcohol in dilution of 1:10). The antigen thus obtained possessed a pronounced specific and relative activity.

The specificity of the antigen obtained by Sakvarelidze was confirmed by a special commission cooperating with the Control Institute of the NKZ SSSR. Solov'yev and Ratner likewise obtained positive results in their experiments with Sakvarelidze's antigen in the complement-fixation reaction as well as the conglutination reaction. (Sakvarelidze's report on the original method of obtaining a foot-and-mouth-disease antigen, which he developed, was published in 1932. For a long time this work did not attract the attention of foreign investigators. Only in five years' time did there appear the report of Kanyo and Olah, who, using alcohol extracts of virus-epithelium, confirmed the data which Sakvarelidze had obtained earlier. German investigators in general have hushed up Sakvarelidze's work.)

Solov'yev prepared, according to Sakvarelidze's method, type-antigens from strains of type O, A, and C virus. As a result of his investigations he reached the conclusion that the foot-and-mouth-disease antigen possesses sufficiently pronounced type specificity and consequently this property of it can be used for differential of types of foot-and-mouth-disease virus. Much later

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Kanyo and Olah likewise applied alcohol extracts of virus-epithelium as a foot-and-mouth-disease antigen for the complement-fixation reaction, and also extracts from the cardiac muscle of infected guinea pigs; but in their experiments they obtained negative results. Following this, they used, as an antigen, virus in the form of macerated epithelium of aphthae of the guinea pig and obtained positive results. For complement-fixation reaction the authors used serum from a human being who had developed foot-and-mouth disease caused by type O virus. Blood was taken on the 20th, 32nd, and 40th day after the beginning of sickness. Complement-fixation reaction with the foot-and-mouth-disease antigen of type O and convalescent serum of the same type was determined to be positive, although not sharply pronounced, while the same complement-fixation reaction with normal human serum was sharply negative.

Helm used centrifugated virus as an antigen for performance of the complement-fixation reaction. He collected epithelium from 24-hour, well-developed aphthae of the guinea pig, ground it with a small amount of physiological solution of sodium chloride and then centrifugated it. In this way Helm prepared type-antigens which he applied in a complement-fixation reaction for differentiation of types of the foot-and-mouth-disease virus. As a result of his research, which he performed with extensive material, Helm reached the conclusion that through using the complement-fixation reaction with type antigens, the types of virus can be completely differentiated.

Galea altered the method of obtaining the virus. He, like

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Helm, used, for preparation of the antigen, virus taken from the guinea pig in the form of the epithelium of aphthae 18 to 24 hours following infection. The epithelium which was collected was ground in a mortar with a small quantity of sand, following which a physiological solution of sodium chloride (pH 7.6) was added to the ground-up mass and then all this was centrifugated at 12-14 thousand revolutions a minute for one hour. The upper portion of the fluid in the centrifuge-tube was antigen. Upon addition to the antigen of a suspension of guinea-pig marrow (1 gram of marrow is ground in 50 cubic centimeters of sterile distilled water) the titre of the antigen increases.

For performance of the complement-fixation reaction, Galea used convalescent serum which had first been deactivated in a water bath at 55 degrees Centigrade for 30 minutes. As a complement (alexin) he used fresh guinea-pig serum. With the prepared antigen the author obtained good results. Krag and Schmidt applied formalinized virus as the antigen for the complement-fixation reaction and also obtained positive results. For preparation of the antigen they used the epithelium of 24-hour guinea-pig aphthae. In convalescent serum obtained from guinea pigs, using the complement-fixation reaction, they observed without particular difficulty complement-fixing substances.

Solov'yev proposed, instead of the complement-fixation reaction with foot-and-mouth disease, the conglutination reaction as more simple in its technique. On the basis of his investigations the author considers it a more sensitive reaction for foot-and-mouth

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disease than the complement-fixation reaction and holds that it gives a lesser percentage of doubtful indications. Peshekhonova and Dobrotvorskaya checked the conglutination reaction with extensive material under conditions of a practical campaign and obtained rather conflicting results, thus placing in doubt the practical value of this reaction. In both cases the authors used type-antigens prepared according to Sakvarelidze's method.

Solov'yev, using the methods of serological reactions, particularly the conglutination reaction, attempted to secure the growth of antibodies in the serums of animals in the process of undergoing the disease and of subsequent hyperimmunization. He actually obtained a curve for the growth of antibodies in the process of hyperimmunization, which rises upward until the first profuse bleeding (10-12 liters). The greatest rise in the curve is noted after injection of the third (last) maximum dose of virus. Following the bleeding a sharp decrease of antibodies in the blood is noted, and following the first "booster" dose of virus they are restored in profusion by the organism. Unfortunately, this extremely interesting work of Solov'yev was carried out with limited material; therefore, it is difficult to say how great its practical value is.

Frenkel obtained negative results in experiments with a virus-agglutination reaction. As an antigen for the performance of the agglutination reaction he applied adsorbed (by means of erythrocytes, kefir yeast, $Al(OH)_3$, and carbon) virus. Upon performance of the agglutination reaction with this antigen and immune serum, and likewise with normal serum, negative results were ob-

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tained in all cases. Consequently, this reaction too has turned out to be unfavorable for the differentiation of virus types.

Certain prospects are inviting with respect to the use of a precipitation reaction. Doronin and Kindyakov, using the original method of Dunin and Popova which they had developed for the purification of plant viruses with specific serums, prepared a foot-and-mouth-disease antigen free of bulk albumins. Upon injection of this into the organism of a rabbit the formation of specific precipitin takes place. Thus, the authors proved the possibility of obtaining a precipitant serum specifically for the foot-and-mouth-disease virus. It would be premature to draw any conclusions as to the practical significance of the precipitation reaction for foot-and-mouth disease, inasmuch as their work has not passed beyond the stage of laboratory research, but the very fact of the obtaining of a specific precipitant serum deserves definite attention. Solov'yev studied the precipitation reaction using as an antigen various extracts -- alcoholic and acetonic -- and also urcantigen (after Tsuverkalov). In all cases the results were negative.

Ascoli proposed a special meiostigmatic reaction which consists in essence of changing the surface tension of immune serum with the mixture in it of liquid antigen , but this reaction has so far not attracted the attention of investigators. Certain investigators have also engaged in the study of non-specific reactions for foot-and-mouth disease.

The experiments of the American commission with a flocculation reaction based on the Sacchs-Georgi method (Sacchs-Georgi, Drejer, Woord, and Bruck) have produced negative results.

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In experiments with the Meinike sedimentation reaction Solov'yev and Peshenkhonova obtained fully satisfactory results. They used as an antigen extract from the heart, liver, and kidneys of swine, from the heart and liver of a hyperimmune bull, and from the heart of a horse (the antigen was prepared according to the third modification of the Meinike method --DMK). Best results were obtained with antigen-extracts from the heart of a pig and that of a horse. On the basis of their experiments authors feel that this reaction may have a certain supplementary significance with respect to the complement-fixation and complement reactions.

In experiments with the Mate-Papakostas formol reaction for foot-and-mouth disease Peshekhonova obtained indefinite results. In a reaction with hyperimmune serums she obtained a rather large percentage of positive indications (81 percent), and at the same time convalescent serum and normal serum gave almost uniform indications. In addition, there was a large percentage of doubtful indications.

The American commission, in experiments with the formol reaction and also with colloidal benzoin, obtained negative results.

Allergic methods of diagnosis of foot-and-mouth disease have not been developed.

PROGNOSIS

Foot-and-mouth disease usually runs its course in the form of a non-malignant epizootic, but at times it assumes a malignant nature and causes mass mortality among stock. In non-malignant

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epizootics, cases of mortality among adult cattle are very seldom observed. Among young animals, especially at the earliest age, a definite mortality is always observed.

Among young cattle (milk-calves) and sucking-pigs foot-and-mouth disease assumes not infrequently a malignant course, causing mass mortality of the young (60-80 percent). Adult, high-producing animals (pedigreed cows) and thoroughbred bulls, and also excessivly well-fed swine, as demonstrated by observation, develop foot-and-mouth disease with considerably greater severity than local low-producing, unimproved stock. Cases of mortality among them are observed considerably more often than among other animals.

In the absence of appropriate zoohygienic conditions, proper feeding, and good and attentive care in the period of sickness, severe complications which are difficult to treat are possible (heart attacks, mastitis and abscesses of the udder, abscesses in the region of the coronary band and the heels, etc.). In pigs and sheep affliction of the extremities is not infrequently accompanied by complete breaking-off of the shoe-part of the hoof if proper veterinary assistance has not been provided in time.

Prognosis in foot-and-mouth disease depends, consequently, to a considerable degree on what conditions make up the environment of the sick animal.

In non-malignant epizootics, especially during the period of pasture-feeding, the prognosis with respect to adult cattle will be favorable. The prognosis should be somewhat cautious with respect to individual, excessively well-fed animals who may suffer

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serious complications and mortality due to cardiac paralysis. As far as very young animals are concerned (milk-calves, sucking-pigs, and nursing lambs), the prognosis should be extremely cautious, inasmuch as this age produces a very high mortality with foot-and-mouth disease.

It is essential, however, to take into consideration the fact that with good care of animals, proper feeding, daily disinfection of buildings, maintenance of the cleanliness of skin areas (the udder, extremities, etc.) and timely provision of therapeutic treatment, losses can be drastically reduced.

FOOT-AND-MOUTH-DISEASE THERAPEUTICS

The treatment of foot-and-mouth disease has so far received little attention. The application of certain measures for treatment has been based on purely empirical data. Meanwhile, the extensive cross-breeding of stock and the raising of high-valued producers and thoroughbreds oblige the veterinarian to use all therapeutic methods to prevent severe and often hard-to-treat complications and mortality of valuable animals.

Therapeutic intervention must be directed above all toward the maintenance and preservation of the heart action. Even with non-malignant cases of foot-and-mouth disease various functional disorders in the heart action are not infrequently noted. With malignant cases prolonged and hard-to-treat functional disorders of the heart action, due to myocarditis (Miocarditis aphtosa), are often observed. Upon development of the disease by stock, greatest attention should be paid to pedigreed cows, thoroughbred producers,

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and fattened pigs. Various complications, involving disorder of the heart action, are most often noted in these animals.

The best remedies in such a case would be tonic preparations (caffeine, camphor, etc.). In cases of the compulsory killing of cattle the meat acquires the odor of camphor, and therefore it cannot always be recommended, at least for fattened animals.

Among specific measures for therapeutic purposes anti-foot-and-mouth disease serum, hyperimmune as well as convalescent, may be applied. The serum produces a therapeutic effect only if it is injected into the sick animal at the very beginning of sickness. Many investigators and practical workers have used milk, casein, serum, etc., for the purpose of treating foot-and-mouth disease.

In its day there was great enthusiasm for protein therapy, which, according to the statements of certain investigators and practical workers (Pavlovskiy, Mashkin, Mikhaylovskiy, Kirsanov, Smirenskiy, Sokolov, and others), yielded supposedly good results with foot-and-mouth disease. Similar indications may also be encountered in foreign writings (Miller and Tun, Dahlenberg, and others). However, upon experimental investigation of the therapeutic effect of milk, those positive results have not been confirmed. Ernst engaged in the study of the therapeutic effect of milk and milk-derivatives (aolan, caseosan), it developing that all these milk-derivatives have no specific effect on the course of the foot-and-mouth-disease process.

In Popova's experiments in connection with research on the effect of milk on cattle for prophylactic as well as therapeutic purposes, negative results were obtained in all cases.

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On the basis of his experiments with the application of milk for therapeutic purposes Ozerov arrived at the conclusion that "injection of milk in cattle produces no positive effect on the course of the disease. Milk does not produce an abortive effect on the course of the disease, either; on the contrary, there was a greater percentage of cows with lingering cases of the disease among those which had been treated with milk than among the control animals". The experiment was performed on 117 head of cattle of various ages. Milk was injected intramuscularly, with the fat removed, following preliminary warming to 92-96 degrees centimeter, in amounts of 80--120 cubic centimeters for adult cattle, 30--50 cubic centimeters for calves.

Skomorokhov and Blazhevich studied protein therapy for foot-and-mouth disease in cattle under conditions of the natural development of an epizootic, and also obtained negative results.

Finzi in Italy applied autohemotherapy for the same purpose. He took blood from sick animals during the period of generalization of the infection, and injected it subcutaneously into the same animals. Finzi declares that this method weakens the course of the infection and causes rapid development of immunity. Into adult animals he injected 150 cubic centimeters, into young animals 50--75 cubic centimeters, into calves 20--25 cubic centimeters. Following injection of blood there was a fleeting thermic reaction (Frehner and Zwick).

For therapeutic purposes Winkler and Teiler injected cattle intravenously with 50 to 100 cubic centimeters of Lugol's solution of

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iodine. With injection of this preparation at the very beginning of the disease the authors obtained good results.

Skomorokhov and Blazhevich have Lugol's solution of iodine for therapeutic purposes in the form of intravenous injections, but the results obtained by them with cattle under practical conditions were not constant. Upon intravenous injection of Lugol's solution of iodine at the very beginning of the disease it was possible to attain very effective therapeutic action. In one case the course of the foot-and-mouth-disease process was perceptibly attenuated, and in another it was even possible to arrest the incipient process at the very beginning of its development and to prevent generalization of the infection.

Over a period of many years Savel'yev obtained great success through the use for therapeutic purposes of Lugol's solution on the larger suburban animal-raising farms. In his opinion application of Lugol's solution during the period of development of a foot-and-mouth-disease epizootic on the farm can even have prophylactic significance.

Shkol'nikov, on the basis of his positive experiment, steadfastly recommends the application of Lugol's solution not only for adult cattle (70 cubic centimeters), but also for calves and pigs (20--30 cubic centimeters, depending on the live weight). Lugol's solution is injected most efficaciously when warmed.

Shkol'nikov applied, for therapeutic purposes with foot-and-mouth disease, intravenous injections of urotropine with caffeine (3 grams of urotropine, 5 grams of caffeine, and 10--15 grams of

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physiological solution per injection), and points to their very beneficial effect on the sick animals's system.

Klimmer adopts a generally critical attitude toward all chemical-therapeutic methods in foot-and-mouth disease. He declared that "in foot-and-mouth disease all chemical-therapeutic methods, including Lugol's solution, are ineffective."

With irritation of the buccal cavity in cattle it is recommended that use be made of disinfectant methods which do not irritate or sear the mucous membrane, specifically: a weak solution (2 to 3 percent) of acetic acid, or a solution of potassium permanganate (1:100), a solution of alum (2--3 percent), or a solution of rivanol in the concentration applied in surgery to the treatment of wounds.

Ratner and Tonigs recommend the application of flavocridin, which facilitates acceleration of the process of recovery and the forestalling of secondary infections. Flavocridin can be used in dilution of 1:500, and also in the form of ointment prepared with vaseline and lanolin. Following treatment with flavocridin foot-and-mouth disease irritations heal rapidly, and on the 2nd to 3rd day after treatment animals usually begin to chew their fodder.

Certain veterinarian-practitioners (Tret'yakov and others) have used 1--2 percent solution of hydrochloric acid to wash out the buccal [redacted] cavity of cattle, and have obtained seemingly good results. We do not recommend the use of this method, particularly in such strong concentrations as used by Tret'yakov.

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Perette steadfastly recommends giving sick animals brewer's yeast or a linseed decoction. According to his data, both these methods have a very good therapeutic effect.

With spread of the disease to the extremities in the region of the coronary band and heels fresh, soft, and clean litter is needed above all in the buildings. Putilov recommends, for foot-and-mouth-disease sickness of stock, the application of peat litter (black sphagnous peat), as possessing good absorption properties, particularly with respect to ammonia. Peat litter is an unfavorable medium for the development of bacteria, (according to Kirsteiner's data, 1 gram of straw contains 115 million bacteria germs, and peat litter one million. This is explained by the presence in peat of humus acid, which possesses bactericidal properties) which often complicates the course of foot-and-mouth disease, particularly with affliction of the extremities and the udder. .There are observations to the effect that with bedding of sick animals on peat litter the irritated extremities and udder heal more rapidly. Peat litter must be recommended in every way wherever there is a possibility.

Disinfection of buildings and stalls where sick animals are housed should be carried out daily. Special "foot baths" with disinfectant solutions may be arranged, and the sick animals may be driven through them once or twice a day. For treatment of the extremities those means may be recommended which are used in general for the treatment of wounds (bandages, drying ointments, powders, etc.) Iensen recommends that the affected parts should be thoroughly washed following removal of loose horny parts and coated with a mixture of tar and cod-liver oil.

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When the udder is affected attention must be turned above all to keeping it clean and to disinfection of the stalls where the sick animal is kept. The teats must be washed with water and soap, dried, and then rubbed with cod-liver oil. For rapid healing of ulcerations on the teats various ointments may be used (boric, zinc, salicylic, flavacridin, etc.). It is recommended that the udder be washed repeatedly with a warm 2--3 percent solution of boric acid. With nervous forms of foot-and-mouth disease, in the case of cerebral irritation Terni advises applying hot water (45 degrees) or an ice-bag on the head and spine. Blood-letting gives good results in such cases.

During the disease major attention must be given to providing the animal with a light, spacious, and well-ventilated building with fresh, soft, and clean litter. In summer animals can be given green grass and concentrates, and during the period of housing in stalls Savel'yev recommends feeding in part with leavened and moistened fodder. Drinking-water should always be clean and slightly chilled. It is desirable to provide the animals themselves with the opportunity to rinse out their oral cavity with clean water, which they do very willingly.

During the period of pasture-feeding a herd diseased with foot-and-mouth disease must be left near open feeding-tanks with clean water, if there are not other population centers in the vicinity, and during the period of confinement in stalls it must be seen that there is always clean, fresh water in the troughs in the barnyard. It is necessary to avoid driving sick animals to pasture during intense heat, and also in bad, raw, and cold weather.

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When the disease attacks the young it is necessary to devote attention to the condition of the stomach-intestinal tract. Upon the appearance of foot-and-mouth disease on the farm, stomach-intestinal sicknesses among the young, in the form of gastroenteritis, can be associated with foot-and-mouth disease.

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CHAPTER VIII

THE EPIZOOLOGY OF FOOT-AND-MOUTH DISEASE

GENERAL DATA

In distinction to many other infectious diseases, foot-and-mouth disease nearly always runs its course in the form of epizootics, spreading over considerable territories. In the past foot-and-mouth disease has sometimes assumed the character of epizootics, (the last panzootic of foot-and-mouth disease, which embraced the whole European continent right up to the shores of the Baltic Sea, was in 1937--1939. It brought enormous losses to animal husbandry in all the countries of Western Europe) which for a brief period have embraced many nations and even whole continents. These peculiarities of foot-and-mouth disease are explained by the strongly pronounced contagiousness of this disease, the existence of a substantial number of types of animals susceptible to it, and the large variety of methods of transmittal and means of spread of infection. Therefore the liquidation of foot-and-mouth disease is always associated with great difficulties.

In many countries of the world foot-and-mouth disease bears a static character, and its liquidation through existing methods of campaigning seems quite problematical.

The static character of foot-and-mouth disease in given localities can be caused either by the existence of foci of infection which have not been thoroughly liquidated or by the systematic transmission of the infection from other contaminated places. Inadequate

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mechanical removal of manure, poor or completely neglected disinfection of barnyards and pig-pens before termination of quarantine, and inadequate cleansing and disinfection of areas adjoining buildings which house animals, facilitate the prolonged outside survival of the virus, particularly in autumn and wintertime. Such permanent foci of foot-and-mouth-disease infection can be the supply bases of various farm organizations, where new stock enters and is infected due to the survival of the virus out-of-doors.

No small role in the creation of such a static character for the disease can likewise be played by convalescents--virus carriers--particularly in cases where herds are replenished yearly on a farm by bringing in new animals from localities contaminated with foot-and-mouth disease.

In certain regions in the East the static nature of foot-and-mouth disease is caused by the presence of permanent infection over the course of a whole year due to the appearance of new-born stock which is free of immunity to foot-and-mouth disease. "In fall adult animals develop the disease, it lasting several months (natural development of the disease); in spring and the beginning of summer infection of calves proceeds (the current year's offspring), and in fall foot-and-mouth disease again attacks the adults" (Terent'yev). In such a case the focus of the infection has a permanent place due to unliquidated external sources of infection as well as to convalescents -- virus carriers.

One of the causes of the static character of foot-and-mouth disease in Central Asia is held by Kindyakov to be particularly its systematic importation from China and Mongolia.

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In many countries a rather regular periodicity (cyclical nature) with respect to the appearance of foot-and-mouth-disease epizootics is noted. In Germany periods of relative "calm" have been noted every 3--5 years, and then a new crest in the epizootic wave advances. Moreover, in individual years great outbreaks of foot-and-mouth-disease epizootics have been noted, followed again by an interval of sharp decline in foot-and-mouth-disease sickness. A definite periodicity in the appearance of epizootics was noted earlier in pre-revolutionary Russia. From data on the trend of foot-and-mouth disease for the period from 1881 to 1912 it is evident that these epizootics reached maximum development every 4 or 5 years.

An explanation of phenomena of periodicity of foot-and-mouth disease epizootics must be sought in the fact that among them mass sickness, both obvious and concealed, of animals susceptible to foot-and-mouth disease takes place; as a result these animals acquire a stable immunity. Following the infection of all animals susceptible to foot-and-mouth disease a gradual "self-extenction" enters the picture, and then a complete termination of the epizootic. The period of complete freedom from the disease lasts until the animals which have had the disease lose their naturally acquired specific immunity, or until more or less complete replacement of the herd, due to newly born animals, takes place.

The time of year and other seasonal factors associated with it do not play an essential role in the spread of foot-and-mouth disease. Many cases are known from practice where foot-and-mouth disease spread with identical intensity in both summer and winter. However, the view has been accepted that when stock is turned out to pasture

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the danger of foot-and-mouth disease increases considerably. In the spread of foot-and-mouth disease there is evidently significance not so much in the time of year as in the intensity of farm traffic (revival of trade in stock and products of animal husbandry, mass movement of animals over cattle trails, supplies of agricultural products, movement of human beings, etc.). Climatic-meteorological factors must also be taken into account, but they have evidently only secondary significance.

Seasonal variations in foot-and-mouth-disease sickness are noted in a whole series of countries (India, China, etc.). Certain investigators are inclined to connect these seasonal variations with the conditions under which animals are kept and particularly with the character of their feeding.

Winkel, on the basis of study of 17 epizootics of foot-and-mouth disease, affirms that between the character of a foot-and-mouth-disease epizootic and the duration of so-called "light" intervals there exists a definite correlation. During prolonged periods replacement of the herd takes place, in consequence of which its susceptibility to foot-and-mouth disease increases, and the epizootic assumes a more intensive and severe, at times malignant, character. During short periods, when animals have still preserved a definite immuno-biological resistance from preceding epizootics, the succeeding epizootic, in Winkel's opinion, will have a non-malignant character.

Still other factors may have an influence on the course of foot-and-mouth disease. Certain investigators, particularly J. Lignieres, affirm that foot-and-mouth disease in wintertime, under

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the influence of the low ambient temperature, runs a considerably milder course than in summer. Our observations completely verify this statement. According to Roemmele's data, under the influence of low outdoor temperature the incubation period in foot-and-mouth disease becomes substantially longer, but in summer, on the other hand, it is considerably abbreviated, and the course of the infection itself is speeded up.

According to Roemmele's affirmation, a temperature of 10 degrees centimeter is capable of restraining the development of primary aphthae, and sometimes even of preventing the onset of generalization of the infection. It is possible, as certain authors suggest, that the humidity in the air and atmospheric pressure also have a definite influence on the development of the foot-and-mouth-disease process. Allendorf suggests that increased heat-transfer through the skin and lungs and the resultant hyperemia create particularly favorable conditions for the multiplication of the virus as an epitheliotropic agent. Cloudiness and slight movement of the air, in Allendorf's opinion, act negatively on the animal's organism, intensifying the effect of moist heat on the system, while cold, dry air, and wind, on the other hand, strengthen the system, increasing the metabolism and its resistance to foot-and-mouth disease. Therefore, with sickness in animals the author recommends giving attention to a constant flow of fresh air and on the provision of the lowest possible temperature. The lowered resistance of an animal's system due to one-sided development (highly milked cows, excessively well-fed pigs) may reflect on the intensity and severity of the epizootic's course. According to Fluckiger's statement, the most severe losses are always caused by foot-and-mouth disease in localities with intensive and one-sided management of animal-husbandry.

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Overexhaustion due to excessive exploitation, prolonged herding or transportation, hunger, various inroads, attrition of the system, and poor living conditions, lower the resistance of the system to foot-and-mouth disease and can involve severe sickness and all possible complications. Turning stock out to pasture in bad weather lowers the natural resistance of the animal's system and facilitates greater severity of an epizootic.

A VIRUS RESERVOIR

An animal sick with foot-and-mouth disease must be regarded as a basic and most dangerous source of infection, capable of giving the virus off into an outer medium in enormous quantities together with all secretions and excretions. Greatest danger from the standpoint of dissemination and accumulation of the virus outside the animal is represented by the secretions of the oral cavity, particularly in the first days of sickness. Secretion together with saliva containing the virus of shreds of epithelium from ruptured aphthae facilitates more prolonged preservation of the virus outside the animal. In the process of development of the disease by a whole herd, particularly when housed in stalls, an enormous amount of the virus accumulates which, in its turn, can influence the severity of the course of the infection itself. From the standpoint of secretion of the virus outside the animal together with saliva, a sick animal must be considered an active and permanent emitter for at least 11 days or 8 days from the moment of generalization of the infection (Waldmann and Reppin).

Emission of the virus with milk is evidently of significance

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only during the period of generalization of the infection; however, independently of this all milk from a herd contaminated with foot-and-mouth disease must be considered to contain the virus and, consequently, may be a source of infection for other animals (calves, sucking-pigs). Emission of the virus with all other secretions, and also excretions (urine, feces) during the period of sickness is of much less significance, but they must also be regarded as sources of infection. Convalescents, as is known, remain as virus-carriers and virus-emitters over a long period.

All agricultural animals which are susceptible to foot-and-mouth disease can become primary sources of infection under certain conditions and consequently natural reservoirs of the virus. Dogs and cats, as animals susceptible to foot-and-mouth disease, also merit certain interest. It is known that they can be infected with foot-and-mouth disease under spontaneous conditions and consequently serve under known conditions as sources of spread of foot-and-mouth disease (Loeffler, Frosch, and Uhlenhuth; Hecker; Albrecht; Galloway; Olitsky; etc.). However, the epizootological role of these animals with respect to the spread of foot-and-mouth disease remains for the time being unstudied. Many contemporary investigators hold that dogs play a much greater role as passive transmitters of infection. They drag from other farms contaminated with foot-and-mouth disease bones or other refuse, for example, following compulsory killing of animals, the remains of poorly buried carcasses of calves or young pigs and also transmit the virus on their skins and extremities. Cats evidently have in general no essential significance either as active or as passive sources of foot-and-mouth-disease infection.

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Many investigators have long been interested in the question as to whether various wild animals, rodents, fowl, and also insects and worms can be reservoirs of foot-and-mouth-disease virus in nature. Long ago the opinion was expressed that wild animals living out of captivity are not reservoirs of virus, and their role in the epizootology of foot-and-mouth disease is conceived as extremely doubtful. Certain investigators, as already pointed out earlier, consider that wild and fur-bearing animals under natural conditions develop foot-and-mouth disease either very seldom or not at all (Edelmann, Stroh, Olt, and Strese, and others) and do not have, consequently, epizootological significance. Elton carried out special observations of wild animals in localities contaminated with foot-and-mouth disease and could not establish any connection between them and the appearance of foot-and-mouth disease among cattle and swine.

However, contrary to all these observations and opinions there is an ever-increasing store of facts which point to the fact that certain types of animals living out of captivity can be infected with foot-and-mouth disease under spontaneous conditions.

In Sweden (1934) during the epizootic of foot-and-mouth disease a dead female elk was discovered under field conditions which exhibited specific affections in the buccal cavity upon pathologo-anatomical dissection. Sallinger reported two cases of clinically established foot-and-mouth disease in roe-deer. Roemmele described a case of foot-and-mouth-disease infection in a mouflon living in the wild state. In Southern Rhodesia a case of disease was noted in an antelope living out of captivity (klein). In Mongolia repeated cases of foot-and-mouth disease under spontaneous conditions were

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noted in antelopes ("dzeren"). Finally, there are known cases of the bringing in of foot-and-mouth disease from Mongolia by antelopes during their migrations into the territory of the Soviet Union. Urbain reported an outbreak of epizootic among the wild animals of the zoological garden in the Vincennes wood (near Paris).

How great is the epizootological role of wild and fur-bearing animals has not yet been established. Doubtless, their role in the epizootology of foot-and-mouth disease can be only secondary, having no serious influence on the spread of foot-and-mouth disease.

From the practical standpoint the hedgehog represents certain interest. He has very high sensitivity to foot-and-mouth disease and can develop it in conditions of spontaneous infection. Edwards described a case of spontaneous infection of a hedgehog on a farm contaminated with foot-and-mouth disease. Following this an experiment was performed with the infection of healthy hedgehogs by cattle under conditions of direct contact, and then of infection of cattle by sick hedgehogs. The experiments verified the possibility of spontaneous infection of hedgehogs. Under the conditions of experimentation Health and Edwards established that in hedgehogs resistance to foot-and-mouth disease increases with a decrease in the ambient temperature. During the winter hibernation, having been artificially infected beforehand, they do not develop foot-and-mouth disease until they wake up. In the tissues of hibernating hedgehogs the virus was discovered on the 28th to 56th day. The authors assume that the virus in the tissues of sleeping hedgehogs can be preserved more than 2 months if they remain in a state of hibernation. The hedgehog, in the authors' opinions, can be a reservoir of virus under known

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conditions. These very interesting data with respect to the hedge-
hog, verified under conditions of experimental test, are in need of
further study for determining the actual role of the hedgehog in the
epizootology of foot-and-mouth disease. We are not inclined to over-
evaluate them, since the small "pilot" experiments performed in our
laboratory have shown that not all breeds of hedgehogs possess such
high sensitivity to foot-and-mouth disease. In Khomenko's experiments
hedgehogs, exposed to artificial infection, developed very mild sick-
ness, and the whole process was limited only to the appearance of
primary aphthae without subsequent generalization of the infection.

Wild rats, as established by the English Commission, are sus-
ceptible to foot-and-mouth disease, but the epizootological role of
these animals is extremely dubious. On the territory of the Pirbright
experimental station and its environs 162 wild rats were caught, 123
of them were investigated by means of infection of guinea pigs, and
in only two cases was the presence of foot-and-mouth-disease infec-
tion verified in the rats (Edwards). Marmots, as shown by Klobouk's
experiments, and also by those of Popova, are susceptible to experi-
mental infection.

In Popova's experiments, which were performed under our guidance,
experimental infection of marmots succeeded with great difficulty, the
disease usually being limited to the appearance of only primary aphthae
on the site of injection of the virus without subsequent generalization
of the infection. There is very little probability that marmots could
play any role in the epizootology of foot-and-mouth disease. The mole,
according to Frenkel's data (Holland), is not susceptible to foot-and-
mouth disease and, consequently, cannot be a virus-reservoir. Field

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mice, as shown by the experiments of Bushe and the English Commission, are susceptible to experimental infection with foot-and-mouth disease, but their role in epizootology seems still more doubtful. Wild fowl are not susceptible to foot-and-mouth disease under natural conditions. Among domestic fowl, certain investigators have succeeded in infecting ducks only. Consequently, wild and domestic fowl cannot be a reservoir of the virus in nature.

In studying the susceptibility of bats conflicting results were obtained, which may stem from the non-uniform sensitivity of various types of bats. According to Edwards' data, bats (Microtus agrestis and Microtus hirtus) possess rather high sensitivity to foot-and-mouth disease. In intramuscular injection of the virus they are infected very mildly and develop sickness with the appearance of aphthae on the tongue. In Torres' experiments, performed in Rio de Janeiro, bats (Desmodus rotundus), on the other hand, were not susceptible to foot-and-mouth disease. Bats could hardly have any significance in the epizootology of foot-and-mouth disease, at least under our conditions.

The question of the possibility of transmission of foot-and-mouth disease by ticks and insects has been given inadequate study. Galloway succeeded in proving that the virus can remain active for 14 days in the system of ticks, but transmissions of the infection by means of tick-bites were not proved experimentally. The experiments were performed on guinea pigs. In principle, nothing new in this respect is furnished by the Hirschfelder's investigations. So far there is no basis for ascribing any epizootological role to ticks.

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Still less understood is the role of insects as possible carriers of foot-and-mouth disease. According to the investigations of Schmit-Jensen, flies (Stomoxis calcitrans) are unable to transmit the virus from an infected guinea pig to a healthy one, even under the most favorable conditions. Stomoxis calcitrans is not an intermediate host, either, since the virus dies rapidly in a fly's intestines. According to Kunioke's data, the virus can remain active for 48 hours on the body of a house fly and for 18 hours in the intestines. But in order to infect an experimental animal with virus from infected flies, he had to be given virus collected from 300 legs and 50 wings. Experiments with infection through bites or the sucking of blood by flies did not succeed in a single instance. In Knese's opinion, insects can play a certain role as transmitters of infection. Burgi, on the other hand, completely denies the role of insects in the transmission of infection from sick animals to healthy ones. Consequently, there are not yet sufficient convincing data for attributing to insects a given role in the epizootology of foot-and-mouth disease.

VIRUS-CARRYING

The question of virus-carrying has long attracted the attention of researchers as well as practical workers. Many data which refer to the existence of virus-carrying have been accumulated in epizootological literature.

As early as 1899, Linquist recited at the VIIth International Veterinary Congress how he had observed several cases of transmission of foot-and-mouth disease by sick animals. Hess reported at the same

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congress that he had observed 7 cases of transmission of foot-and-mouth disease by sick animals in 28 to 139 days following removal of quarantine.

In subsequent years many other authors also noted cases of transmission of foot-and-mouth disease by sick animals (Melchers and others). In 1904 Kendziorra observed a case of transmission of foot-and-mouth disease around Anklam (Germany) by animals which had been used experimentally by Loeffler and had been returned in three months to the owner. Migge and Marks reported an outbreak of foot-and-mouth disease around Ostered (Germany), which took place in their opinion following the shipment there of a bull which had developed foot-and-mouth disease 2½ years before. Bang described a case of transmission of foot-and-mouth disease in Sweden by a bull which had been transported from Holland. Rudovskiy observed an outbreak of epizootic in Moravia, which took place after healthy stock had been shipped together with diseased animals.

In England in 1924 several cases were recorded of transmission of foot-and-mouth disease by animals which had earlier been diseased. In one case an outbreak occurred after 2 head of cattle had been received which had developed foot-and-mouth disease 8 months before. In another case an outbreak took place after a farm had acquired a bull and a heifer which had developed foot-and-mouth disease 4 months before.

In an English village Forgeot observed a case of transmission of foot-and-mouth disease by an animal which had developed the disease 6 months earlier. Pineteaux and Burbon report a case of virus-carrying

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where a heifer which had developed the disease in April and was transferred to an uncontaminated herd in August, was the cause of an outbreak. The heifer itself was immune to foot-and-mouth disease. All other sources of transmission were excluded in this instance. The locality where the heifer had been brought had been free of foot-and-mouth disease for several years.

In Switzerland during the period 1919--1923, 408 outbreaks of foot-and-mouth disease were recorded which had been caused by virus-carrying (American Foot-and-mouth-disease Commission).

In Prussia, beginning with 1908, there was an account of "continuing virus-emitters", numerous cases having been recorded of outbreaks of epizootic caused by animals which had earlier developed foot-and-mouth disease. Outbreaks of epizootic on uncontaminated farms due to virus-carrying have also been noted repeatedly in a number of republics and oblasts of the USSR.

In spite of such convincing data, accumulated in the course of many decades, with respect to virus-carrying in foot-and-mouth disease, this question remained for a long time in dispute, inasmuch as there was no direct experimental proofs.

The first attempt at experimental study of virus-carrying was performed by the American Foot-and-mouth-disease Commission. The experiment was organized at Alfort (France) in 1926, with the participation of prominent French investigators. Twenty-seven animals needed for the experiment (20 which had developed foot-and-mouth disease and 7 which had not) were sent from Switzerland; the remaining animals, known not to have developed the disease and consequently susceptible

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to it (35 head of cattle and 4 pigs), were purchased in France, in a locality known to be free of foot-and-mouth disease. The cattle delivered from Switzerland were convalescents suspected of being virus-carriers. They had developed foot-and-mouth disease at various times, and 58 to 234 days had elapsed since recovery. As a result of direct and prolonged contact (56-87 days) of the once-diseased animals with those which had not been diseased, not a single animal from the ranks of the 35 head of cattle and 4 pigs developed foot-and-mouth disease. In addition, bile was taken from 13 animals which had had the disease and injected subcutaneously in 16 other head of cattle. All these remained healthy following injection of the bile. Finally, from the 10 head of cattle which had retained certain traces of irritation on the extremities (cracks, cavities, etc.) material was taken and injected into the mucous membrane of the oral cavity of 6 head of cattle. All these remained healthy. And in only one case, when guinea pigs were infected with material from once-diseased animals, was infection with foot-and-mouth disease successful. The material in this instance was taken from an extremity which had been afflicted with foot-and-mouth disease 54 days earlier. In general it may be considered that negative results were obtained in the experiments of the American commission on the study of virus-carrying.

In experiments with the study of virus-carrying in cattle, Lebailly also reached negative conclusions. He brought 62 head of cattle which had developed foot-and-mouth disease and had been collected from various farms to a farm uncontaminated with foot-and-mouth disease, where there were 450 head of healthy cattle which had not earlier had foot-and-mouth disease. As a result, direct contact of both these groups of animals did not cause an outbreak among the

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animals which had not had foot-and-mouth disease. These data of American and English investigators cast doubt on facts of virus-carrying which have long been noted in practice.

Somewhat later Waldmann, Trautwein, and Fyl, on the basis of experimental investigations with respect to virus-carrying with foot-and-mouth disease, reached a completely different conclusion. They proved, for extensive experimental material, that virus-carrying is a fact of sufficient scientific foundation. They performed their investigations on guinea pigs and cattle. It turned out that virus can be proved in the blood of guinea pigs which have developed foot-and-mouth disease during a period of 2 to 110 days. In extract from the kidneys and urinary bladder of guinea pigs the virus was observed in several tests on the 8th, 10th, 11th, 13th, 15th, 17th, 48th, 60th, and 94th day. Experiments performed on cattle verified the results obtained in experiments with guinea pigs. Five hundred head of cattle were used for experiment. Virus was proved in the blood of 2.6 percent of stock which had developed foot-and-mouth disease in 33 to 58 days after infection. In addition, of 8 head of cattle (whose blood had exhibited the virus) the urine of 6 animals contained virus for 8 to 146 days following infection. In individual cases it was possible to observe virus in the urine of hyperimmune bulls for 246 days. At the same time it was also proved that emission of virus with the urine can take place even when it is not present in the blood.

In convalescent serum the presence of the virus was proved on the 38th day following infection, and in guinea-pig serum on the 7th to 24th day following infection. The experiments of Waldmann, Trautwein, and Fyl were performed with the method of accumulating the virus through absorption.

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In the National Scientific-Research Medical Institute in England a series of experiments were performed on the study of virus-carrying with the absorption method of accumulation of the virus (as was done in the Riems Institute). The results thus obtained were negative. The authors consider that urine, being alkaline or acidic, is generally unfavorable for such experiments, and therefore such experiments offer no interest. Somewhat different results were obtained with study of this question by the English Commission on Foot-and-mouth Disease.

In the English Commission's experiments virus was discovered in the urine of one cow at the 63rd--69th hours following infection, in that of another in 165 hours (3 days after its presence could no longer be proved in the milk and blood), and finally in that of a third cow the virus was not observed at all. In the organism of a guinea pig it was possible to prove the virus' presence for a maximum of 11 days following infection.

The English Commission on Foot-and-mouth Disease, on the basis of its experiments, cast doubt on the data on virus-carrying of investigators of the Riems Institute. And nevertheless, numerous practical observations indicate that virus-carrying in foot-and-mouth disease is an indisputable fact.

The question of localization of the virus in the organisms of sick animals has been given inadequate study. Loeffler considered that the virus in the organisms of sick animals is found "in the mucous membrane of the channels of access". Zschokke, Bohm, and Assel affirmed that the virus is localized principally in cracks and cavities

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of the shoe-part of the hoof, where it can remain in concealed form for 5 to 6 months, and in some cases even up to 12 months, and, as the shoe-part of the hoof wears down, is cast outward. Incidentally, Hess was one of the first to state the assumption that the virus can be preserved for a long time in the shoe-part of the hoof of animals which have become diseased.

De Blieck and Winkel report that they succeeded experimentally in verifying the correctness of the "hoof theory" in foot-and-mouth disease. They infected a healthy animal with material obtained from the hoof of an animal which had developed foot-and-mouth disease three weeks before. Burgi was also a great partisan of the "hoof theory".

However, this theory is not now generally acknowledged and is disputed by many investigators. We have already indicated that the American Commission on Foot-and-mouth Disease was essentially unable to confirm this "hoof theory". In his experiments with infection from material from the shoe-part of the hoof of animals which had developed foot-and-mouth disease 2 to 3 months before, Lebailly obtained negative results. Brandt (Riems Island) checked the "hoof theory" experimentally with extensive material, and only in one case succeeded in infecting an experimental animal, which the author himself is inclined to attribute to inadequate observation of the conditions of the experiment.

In Brandt's experiments there were 103 bulls and 8 pigs, used for experiment following development of the disease: the bulls from 12 to 159 days and the pigs from 5 to 123 days following infection. As a result of his experiments Brandt drew the following conclusion:

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"Animals which have developed foot-and-mouth disease can be virus-carriers only in very infrequent instances. The correctness of the hypothesis of the preservation of the foot-and-mouth-disease virus in the shoe-part of the hoof should be considered not proved".

If such localization of the virus took place, it would be of very small practical significance.

Howart, Busch, and Terni proved the presence of virus in the myocardium and intestines. Burgi assumes the survival of the virus in the digestive tract and in particular on the mucous membrane of the rumen, where aphthae and erosions develop not infrequently and erosions remain without healing for a long time.

It is inherently obvious that far from all virus-carriers are virus-emitters, but from the practical standpoint all virus-carriers represent indubitable danger to the surrounding medium.

In the experiments of Waldmann, Trautwein, and Fyl with cattle, virus-carrying was proved in only 2.6 percent. Burgi considers that the proportion of virus-carriers is not greater than 3 percent of the overall number of animals which have developed the disease. In Fluckiger's opinion, virus-carriers must be reckoned as only a few percent in all. Olitsky considers virus-carrying as only a special case, from which a rule should not be formulated. Forsman and Magnusson are inclined to deny completely the epizootological role of animals which have been diseased.

From the practical standpoint it is very important to know how long virus-carrying can last and whether it is permanent or the virus

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is emitted from the system only periodically. Epizootological observations on virus-carrying have been performed in Switzerland. According to the data of such observations during the period from 1919 to 1923, virus-carrying can last 5 to 6 months.

At the XIIth International Veterinary Congress, Fluckiger declared that emission of the virus with the urine by animals is possible several years following development of the disease. However, as it seems to us, a very cautious attitude should be adopted toward this declaration. In confirmation of his conclusions on the duration of virus-carrying with foot-and-mouth disease Fluckiger cites the following examples from Swiss practice: (1) for the first time on November 16, 1920 and for the second time on November 16, 1921; (2) for the first time in May, 1926 and for the second time in June, 1927; (3) for the first time in June, 1927 and for the second time in June, 1928. In the first case a calf which had been born in January, 1927, and which had not previously had foot-and-mouth disease, developed the disease. In the second and third cases outbreaks of foot-and-mouth disease took place as the result of adding once-diseased animals to the herd. The duration of virus-carrying in the first case was 12 months and 6 days, and in the second 13 months.

Rudovskiy assumes that the duration of virus carrying ranges from 9 to 13 months, Hofistetter up to 127 days, and Migge and Marks up to 2½ years.

In their day, Kling and Hojer expressed the assumption that man can be a virus-carrier. In confirmation of this they cite their investigations, through which they supposedly succeeded in proving

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this for monkeys. The latter, according to the authors' data, emitted the virus into the surrounding atmosphere for 49 days following infection. Kling reports that he succeeded in proving the presence of virus in the contents of the bowels of a man who had lived in an infected locality and had drunk raw milk.

The results obtained by Kling and Hojer for monkeys were checked by Waldmann by means of investigation of the saliva and blood of human beings which had had direct contact with sick animals. The results obtained were negative.

Thus, although large-scale and diverse materials have been accumulated on the question of virus-carrying with foot-and-mouth disease, its epizootological significance, however, has been given inadequate study. In practice, then, it is necessary to consider virus-carrying and to establish definite restrictions with respect to animals which have had the disease.

PASSIVE TRANSMITTERS

Not only domestic animals and fowl, but also man, can be passive transmitters of foot-and-mouth-disease infection. In the epizootology of foot-and-mouth disease one of the first places must be given to man as a passive transmitter of infection. Unfortunately, in practice the role of man as a passive transmitter of infection is not fully appreciated. Meanwhile, there are available numerous examples from foreign practice as well as from our own Soviet practice where man has definitely been a cause of the bringing of foot-and-mouth disease to a farm. Special danger in this respect is represented by people who care for sick stock, and also by supply

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personnel, who often violate rules of veterinary and sanitary practice.

Finally, individual cases are known where veterinary workers themselves were the cause of communication of foot-and-mouth disease to uncontaminated farms. It is very often difficult to expose the role of individual passive transmitters, particularly during the period of storage, grain delivery, and field work. Thus, for example, Veterinary Doctor Lapteve reports that foot-and-mouth disease was brought to one kolkhoz by grain transports during grain delivery. In this case, the transmitters of infection could have been human beings and animals, and finally, vehicles. Such examples, unfortunately, are not alone. Instructive in this respect is the experiment in fighting foot-and-mouth disease in Switzerland, where, according to Burgi's reports, the quarantine is extended not only to animals which are sick and suspected of infection, but also to human beings who live on farms contaminated with foot-and-mouth disease. And only when these human beings have absolutely not been in direct contact with sick animals can they with the authorization of veterinary bodies move to other places, prior disinfection of the strictest order being obligatory. (From Burgi's report at the session of the International Epizootic Bureau in Paris in 1926.)

Burgi considers that during an epizootic all relations among human beings must be submitted to the strictest control and kept to the minimum. Due to these considerations, all commerce must be forbidden. Without specific authorization by the authorities inhabitants should not leave or enter localities which are under quarantine. In Denmark,

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persons living on the territory of farms contaminated with foot-and-mouth disease are forbidden to visit churches, schools, and also any kind of meetings in general. In Sweden all persons arriving from another country are forbidden for 6 months to enter into contact with cloven-footed animals, if these persons have not previously passed through special medical examination and disinfectant treatment. In the US examination of cattle upon suspicion of foot-and-mouth disease is performed without inspection of the buccal cavity, but on the basis of certain external clinical symptoms only.

Among domestic animals the horse can be a passive transmitter of infection.

One case is known, which we have already cited before, where virus was brought into a population center in the hair of a horse's mane, causing an outbreak of foot-and-mouth disease (Francke and Noertler). The fact itself of the possibility of survival of virus on the outer parts of an animal is disputed by no one at present. The virus can be transported also on the hoofs of a horse together with manure and dirt which adhere to them.

Among other domestic animals the dog may be a passive transmitter of infection. During epizootics serious attention must be paid to dogs.

Fowl, as said already, are not susceptible to foot-and-mouth disease, but the role of mechanical transmitters has been attributed to them. In particular, in England it was long held that foot-and-mouth disease was brought into the territory of the country by fowl from the Continent (Stockman). It was assumed that they could carry the virus

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on their plumage, feet, and bills. However, in the course of further study of foot-and-mouth-disease epizootology it was established that the cause of communication of foot-and-mouth disease to the territory of England was mainly the import of frozen meat from colonies contaminated with foot-and-mouth disease. Burgi also denies any role for fowl in the epizootology of foot-and-mouth disease.

However, there are other data pointing to fowl as mechanical transmitters of the infection. Robinson, describing one of the outbreaks in England, cites evidence with respect to a definite connection between outbreaks on the continent in 1937 and the autumnal migrations of birds.

Bullough associates the outbreaks of foot-and-mouth disease in Great Britain, Finland, Sweden, and Denmark which have taken place in recent years with the travel and migration of starlings. In the magazine Farmer Stock-Breeder (1938) empirical observations are cited with respect to starlings, which supposedly were transmitters of foot-and-mouth disease from Germany and France to Great Britain. Hejbel affirms that crows are extremely dangerous spreaders of infection. These affirmations are based on practical observations.

In determining the causes of an outbreak of foot-and-mouth disease among cattle belonging to inhabitants of a certain city (1940), and also of a simultaneous outbreak in its vicinity, we were convinced that crows can sometimes actually be carriers of infection. At a meat combine during mass compulsory slaughter of sick stock which had been sent in by railroad, the ground-area of the trust was heavily soiled with manure and remnants of fodder, following unloading of the

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stock from freight-cars. Piled in a heap in the open, manure from places where the sick stock had stood before slaughtering attracted a large number of crows. As a result, an outbreak of foot-and-mouth disease occurred simultaneously among stock in the city and belonging to the neighboring population within a radius of 2 to 6 kilometers. All other sources of communication were excluded in this case.

Fowl, which have long been considered long-distance transmitters of foot-and-mouth disease, evidently do not play an essential role in the epizootology of foot-and-mouth disease. Further observation and experimental proof are needed.

THE PRODUCTS OF ANIMAL HUSBANDRY

Among products of animal husbandry which represent greatest danger as sources of spread of foot-and-mouth disease, it is necessary to single out the meat of compulsorily slaughtered sick animals, milk and milk products originating on farms contaminated with foot-and-mouth disease, various meat refuse (bones, feet, stomachs, etc.), and finally, by-products (hides, fleece, horns, hoofs, etc.). The possibility of communication of foot-and-mouth disease by rapidly chilled and frozen meat has been proved by a whole series of experimental data (English Commission on Foot-and-mouth Disease, Schlegel, Lourens, Makarevich, Skomorokhov, etc.). The virus in meat, as indicated earlier, can die only in the process of aging of the meat under the influence of lactic acid.

In 1926 a severe outbreak of epizootic occurred in Scotland,

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caused by pig carcasses delivered from Europe for the manufacture of bacon. The presence of virus in the carcasses was verified by the laboratory of the Ministry of Agriculture. Many other outbreaks in England, whose causes remained unexplained at the time, are evidently explained also by transfer of the infection together with imported meat delivered in frozen form from countries contaminated with foot-and-mouth disease (Argentina, Brazil, Uruguay). Similar instances of communication of the infection with meat take place considerably more frequently in practice than is described in literature on the subject.

Various refuse and odds-and-ends which follow the slaughter of animals killed compulsorily can be a source of communication of foot-and-mouth disease to a farm. The sale of bones, feet, and stomachs from animals killed without preliminary veterinary inspection very often serves as the cause of the spread of foot-and-mouth disease.

Andrewes fed swine with pulverized bones together with bone marrow from sick animals, after they had been stored at 1.6 degrees Centigrade for 80 days, and thus caused foot-and-mouth-disease sickness. In the experiments of Minett cited earlier it was always possible to cause foot-and-mouth-disease infection through feeding swine with bone-marrow, containing the virus, together with pulverized bones, after the marrow had been stored at 4 degrees Cent.grade for 42 days.

According to law in England meat refuse can be given to swine as fodder only after preliminary sterilization.

Mohler (US) once reported that the cause of the outbreak of foot-and-mouth disease in California in 1929 was meat from Buenos

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Aires (Argentina) which had been delivered 57 days after shipment. Upon unloading of the incoming steamship and partial transfer of the meat carcasses to another steamship, the carcasses were cleaned and trimmed. After cleaning of the steamship scraps of meat and meat-rinds were thrown ashore, and there an unidentified old man gathered them into a bundle and subsequently sold them as meat refuse and odds-and-ends to a farm for feeding to pigs. Following feeding with this meat refuse and odds-and-ends an outbreak of foot-and-mouth disease occurred among the pigs on the farm, and in sequel the foot-and-mouth disease spread rapidly farther. A similar instance of communication of foot-and-mouth disease in the US happened in California and Texas in 1924-1925.

Churilov (1929) reported two cases of infection of milk cows following the drinking of water in which meat purchased in a meat shop had been rinsed. The cows took sick on the 3rd or 4th day after they had been given the meat-water to drink.

We observed an instance of an outbreak of foot-and-mouth disease in a leading suburban pig-raising farm after the stomachs of ruminants had been delivered there from a meat combine for processing into pig feed. Now that many investigators (Skryabin, Kallert, Ioest, Skomorokhov, Akulov, etc.) have proved the presence of specific afflictions in the forward sections of the stomach of ruminants, all stomachs from animals sick or suspected sick with foot-and-mouth disease should be regarded as an extremely dangerous source of infection.

Leather materials, when treated with brine as well as dry, can serve as a source of the spread of infection. It has been proved

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experimentally that in hides preserved with sodium chloride the virus can preserve its activity for 46 days (English Commission). Drying, as is known, makes the virus still more resistant and able to exist for an extremely long time. Consequently, leather goods from regions contaminated with foot-and-mouth disease must be regarded as a possible source of communication of the infection. Morgan states that foot-and-mouth disease has been brought to England from Argentina mainly with imported hides in which the virus was able to exist for a very long time. (However, Morgan's statements are based largely on his personal "deductions", have been confirmed by no one, and must be regarded in a very critical light.)

The possibility of prolonged survival of the virus on the hide is disputed by no one. According to data of the English Commission, the virus can remain active for 28 days on the hide of cattle. It can, as indicated earlier, be preserved in cracks in the hoofs, and, in addition, the hoofs can be polluted with virus by purely mechanical means. Bohm states that he succeeded in causing infection in experimental animals with material prepared from scraps of the hoof-horn of animals which had developed foot-and-mouth disease 8 months before. These statements of Bohm seem to us of little probability. However, there is no basis for considering hoofs of sick animals completely safe with respect to the possibility of communication with them of infection.

Milk and milk products prepared from delivered or commercial unboiled milk are also not infrequently a source of communication of foot-and-mouth disease to a farm. A particularly great danger is represented by the feeding of stock with so-called "leavings" from

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artel-operated meat and cheese factories, which may receive unsterilized milk during foot-and-mouth-disease epizootics. The capacity of the virus for prolonged survival in milk is adequately founded on experimental data. In milk chilled directly after milking the virus can remain active for 15 days at 4 degrees Centigrade, and dies only when the milk sours. In dried milk the virus is preserved for a still longer time. In fresh butter prepared from unboiled (separated) cream, and also in salt-butter, the foot-and-mouth-disease virus is preserved for a very long time (English Commission). During foot-and-mouth-disease epizootics in Sweden dairy establishments have often been the chief cause of intensive spread of foot-and-mouth disease (Kjerrulf).

In Denmark in 1925-1926, at the very beginning of an epizootic, the tightest restrictions were imposed with respect to milk-processing factories, which made it possible to inhibit the spread of foot-and-mouth disease. At that time only 6 percent in all of stock were attacked by foot-and-mouth disease in Denmark. But as soon as all these restrictions with respect to dairy establishments were relaxed, for a very short time about 50 percent of all stock were attacked by foot-and-mouth disease. During one epizootic of foot-and-mouth-disease in Sweden Kling and Hojer observed repeated outbreaks caused by milk products.

In instructions and admonitions on fighting foot-and-mouth disease the fixing of a restriction with respect to milk and milk products from farms contaminated with foot-and-mouth disease is usually envisaged. Following preliminary on-the-spot sterilization

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milk and milk-products do not represent danger as food-products, but any connection with a contaminated farm, even though it may be effected under veterinary supervision, risks greatly the spread of infection. For this same reason the closing of meat and cheese factories and milk-collection points located in the threatened zone is of extreme expediency right up to the removal of all restrictions with respect to foot-and-mouth disease.

In literature on the subject, numerous cases have been described of foot-and-mouth-disease sickness in children occasioned by use of raw milk from sick animals. In cities many cases of sickness in children through use of market milk during epizootics have been recorded. Rosenberg, as already indicated earlier, observed a number of sicknesses among human beings caused by butter containing virus. Such cases are recorded especially often in veterinary practice when calves and sucking-pigs are fed milk from farms contaminated with foot-and-mouth disease. Milk and milk products from contaminated farms must be regarded as a possible and extremely dangerous source of infection.

FEEDS AND FODDERS

In the epizootology of foot-and-mouth disease rather great significance is possessed by various fodders, mainly by the coarse ones. The possibility of prolonged survival of the virus in fodders has been proved by numerous experimental data. In hay, as shown by the experiments of the English Commission, the virus can survive up to 56 or 108 days under certain conditions. In direct experiments with infection of calves it was established that hay contaminated with virus causes sickness in calves in one month after feeding of it to them. By his day

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Hecker had declared already that the virus can be preserved up to 6 months on dried hay.

The possibility of spread of foot-and-mouth disease through hay contaminated with virus was verified in Kindyakov's experiments. In his experiments, as indicated earlier, the virus, depending on the time of year, was preserved from 3 to 10 days on the surface of a haystack (September--October), and within the haystack it could remain active for a month (June--August) and in autumn-winter weather for 105 to 200 days.

We know of several cases from practice where hay brought from one locality to another several months after removal of quarantine caused outbreaks of foot-and-mouth disease upon feeding to stock on non-contaminated farms. Incidentally, in England a law is still in force which prohibits importation of hay from countries which are not free of foot-and-mouth disease. The law also says that hay used for packing must not later be used for feeding to stock, but is subject to destruction. Evidently the same restrictions must be imposed with respect to straw. From experimental data it is known that the virus can be kept active on straw for 2 months.

In silage the virus perishes very rapidly, as shown by the experiments of Belogorskiy and Lipatov performed in our laboratory.

The possibility should not be excluded of communication of foot-and-mouth disease with concentrated and mineral feeds (bran, flour, meat and bone meal, etc.). It has been proved experimentally that the virus can survive in bran for 56--140 days and in mash for 14-49 days. There are no experiments with respect to bone and meat

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meal which confirm any degree of danger upon the feeding of them to animals. However, it has been proved that the virus can be preserved up to 107 days in the marrow of animals slaughtered during the fever stage. Andrewes fed pigs with bone-marrow and pulverized bones which had been stored for 50 days at 1.6 degrees Centigrade. As a result all pigs, as a rule, developed foot-and-mouth disease. Similar experiments were performed by Minett, who fed pigs with bone-marrow and pulverized bones which had been kept at 4 degrees Centigrade for 40 days, and the pigs, as a rule, also developed foot-and-mouth disease.

In a number of countries (US, England, etc.) particular attention is also given to the containers in which concentrated fodders for stock and likewise meat or other products for consumption, are transported from other countries. In England, for example, the law forbids the conversion into bags of cloths in which meat has earlier been wrapped, and the use of these bags as containers for agricultural products and feeds.

PASTURES AND WATERING-PLACES

Interesting data with respect to the possibility and duration of survival of the virus in pasture conditions were obtained by Kindyakov. According to his data, the virus is preserved out-of-doors for a rather prolonged time in the summer, and particularly in the autumn, months. On the moist surface of the earth the virus, in Kindyakov's experiments, was kept viable for 5--7 days in August, 11--15 days in September, 15--20 days in October, and on the stalks of plants for 24 hours in July-August, 2--6 days in September,

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8--10 days in October, and finally, 52 days in November--December.

In Trautwein's experiments the virus, in the form of the epithelium of aphthae, remained active for 67 days out-of-doors-- in the air, under the action of light, sun, and other factors of exposure- and for 11 days on sandy soil. In the English Commission's experiments it was active in garden soil up to 25--30 days.

The data with respect to resistance of the virus out-of-doors obtained by Kindyakov, Trautwein, the English Commission, and other investigators, provide a basis for drawing the conclusion that it can be preserved for a rather long time in pasture conditions. The duration of its survival in pasture conditions will depend on very many conditions: on the intensity of sunlight (ultraviolet and infrared rays), the temperature of the out-of-doors, the degree of drying of the virus itself and of the base on which it is located, etc. It may be stated that in the southern regions of the USSR (Georgia, Abkhazia, Armenia, Azerbaydzhan, etc.), and also in the East (in Kazakhstan, Tadzhikistan, Turkmenistan, etc.) a rather rapid sterilization of the pasture should occur due to the abundant ultraviolet and infrared radiation and partially due to the high outdoor temperature. On the other hand, in northern regions where the number of sunlit days is small, a more prolonged survival of the virus on a pasture is possible. When temporary termination of pasturage in various parts of the pasture is necessary, it must be based on the aggregate of all factors capable of influencing the length of survival of the virus out-of-doors.

It seems to us that the epizotological significance of the pasture in foot-and-mouth disease is none-the-less small, at least

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in regions which have a large number of sunlit days a year.

With respect to the degree of danger of drinking-water vessels as possible sources of spread of foot-and-mouth disease there are very few indications available in contemporary literature. According to data of the Riems Institute, the virus can keep its activity in fresh water up to 40 days and in salt water up to 100 days. However, these data, obtained under laboratory conditions, are not adequate to be extended to survival of the virus in stream-fed water tanks and lakes. Fluckiger states that if the virus is taken in the form of epithelium of aphthae and placed in river water without any protective arrangements it very rapidly loses its virulence under the influence of mechanical, biological, and bacteriological factors in the water. He considers that the possibility in stream-fed watering places of bacteriophage which destroys the virus is not excluded. (The phenomenon of the action of bacteriophages must be considered so far to be unproved with respect to the foot-and-mouth-disease virus.) Observations over the course of many years with respect to the role of stream-fed watering places as sources of the spread of foot-and-mouth disease, performed in Switzerland, have given Fluckiger a foundation for stating that streams have no significance in the epizootology of foot-and-mouth disease. Burgi considers that rivers and brooks beyond a doubt do not play any essential role in the spread of foot-and-mouth disease.

At the time of our expedition (Skomorokhov, Popova, Krasovskiy, Ovsyannikov) in 1928 we also had an opportunity of becoming convinced that stream-fed drinking places, even when the water flows very slowly, cannot serve as a source of the spread of foot-and-mouth disease. In our case two herds, of which one developed foot-and-mouth disease

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and the other remained healthy, were pastured simultaneously along opposite banks of a small river in the summertime. They collected at the watering-place at almost the same time of day and in a single place, remaining only on the opposite banks, and infection still did not occur through the water. Evidently no one has yet engaged in study of the possibility of prolonged survival of the virus in the salt water of lakes and in ascertainment of the epizootolog[redacted] of these watering-places.

A somewhat different attitude must be toward small watering-places with standing water and, particularly, toward wells put to common use. In this case the danger will doubtless be greater. In such instances attention must be paid mainly to buckets and tubs with which water is poured and to troughs from which animals drink.

With respect to the prevention of the spread of foot-and-mouth disease through small watering-places and wells the general veterinary and sanitary measures which are recommended with respect to other infectious sicknesses are completely adequate, as we shall see later on.

MANURE AND WASHINGS FROM MANURE

Under certain conditions the virus can be preserved for a very long time in manure and the washings from manure. A particularly great danger from the point of view of dissemination of the virus is represented by dried and frozen manure. The virus perishes in 6--9 days in manure at a depth of 30--50 centimeters; on the surface of manure piles it can remain active up to 28 days (Wagener). According to Kindyakov's data, in frozen manure piled in a dung-heap the virus

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can be preserved 156--160 days in winter-time. During the warm season, on the other hand, as early as the 29th--31st day from the moment of a warm spell out-of-doors it perishes under the influence of decomposition of the manure.

Manure and all refuse following the unloading of animals from freight-cars should be regarded as possible and very dangerous sources of infection. Manure from contaminated farms cannot be used, without preliminary biothermic disinfection, for any farming or other needs, and in addition must be disposed of beyond the confines of the farm.

In visiting contaminated farms it must always be remembered that infection can very easily be communicated to another farm with manure particles. Savel'yev (1928) observed in one of the suburban farms repeated instances of the transmission of foot-and-mouth disease with manure delivered from the unloading area of a meat combine for the improvement of the farm's fields and kitchen garden. The washings of manure represent undoubted danger with respect to the spread of foot-and-mouth-disease infection.

In the washings of manure of open sewage canals the virus can remain active up to 9--15--39 days, and in winter, when processes of decomposition are retarded, it does not lose its activity for 103 days (Wagoner). Therefore, it is necessary that manure washings on farms be collected in hermetically sealed receptacles, and only after disinfection can it be used for various farming needs.

The question of the length of survival of the virus in buildings (cattle-sheds, enclosures, pig-pens, etc.), where sick animals have been kept, has so far been given insufficient study. In Lebailly's

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experiments (Pirbright experimental station) cattle were placed in a stall where animals sick with foot-and-mouth disease had been kept two or three days before, and infection of the experimental cattle still did not occur.

Magnusson (Sweden) checked Lebailly's experiments and reached the conclusion that the spread of the infection by means of buildings and stalls where sick animals have been previously kept evidently occurs infrequently and principally during the cold time of year.

In certain countries (US, Switzerland) there are in effect very strict regulations with respect to buildings contaminated with virus. For example, animals can be placed in buildings where there have been sick animals no sooner than 30 days following elaborate mechanical cleaning and thorough disinfection. In some countries of the East (Mongolia, China, etc.), and also in colonial countries where cattle are pastured the year around in the open or kept in primitively constructed "bases", the virus keeps its activity in wintertime for a very long time and remains until spring itself and even summer.

CATTLE MARKETS AND TRANSPORTATION OF ANIMALS

Cattle markets (Bazaars) have always been one of the most serious factors in the epizootology of foot-and-mouth disease. In view of the exceptional contagiousness of the foot-and-mouth-disease infection only one diseased animal is sufficient for infection of a considerable portion of the market cattle. In addition, such a diseased animal will be a source of dispersal of the virus wherever it goes. The possibility of preventing such instances, even with the provision of veterinary inspection, is excluded because the animal can be

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brought to market at the very beginning stage of development of the foot-and-mouth-disease process, when there may be no visible clinical symptoms. The animal may also be brought from remote points while still in the stage of incubation.

Therefore, attention of veterinary-inspection bodies must be concentrated not only on surveillance of the cattle of farms contaminated with foot-and-mouth disease, but also on surveillance of the cattle of farms which are threatened. Especially great danger is represented by cattle suspected of disease, inasmuch as it is difficult to spot cattle afflicted with foot-and-mouth-disease in the very beginning stage. They can be very active sources of infection and at the same time escape the attention of veterinary-inspection bodies.

Individual veterinary inspections of cattle at markets also involves to a certain degree some risk of mechanical transmission of the infection in the process of inspection of the cattle. Therefore, following inspection of each animal the veterinary worker is obliged to disinfect his hands with a solution of caustic soda or formalin. It is still better to refrain entirely from mass inspection of the buccal cavity for the purpose of exposing foot-and-mouth disease. When a sick animal with clinical symptoms of the disease penetrates to the market it will be easy to distinguish it without inspection of the buccal cavity.

In certain countries (US, Sweden, etc.) when foot-and-mouth disease is suspected there is a general prohibition of inspection of the buccal cavity of animals due to the danger of spread of the infection. Upon suspicion of foot-and-mouth disease American veterinarians inspect cattle without touching it, remaining at some distance, usually on horseback.

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Great danger with respect to the spread of foot-and-mouth disease is represented by any feed remnants and leavings which remain following the closing of markets and bazaars, and also by manure.

In foreign countries cattle markets are a basic hotbed of all infectious and, in particular, acutely infectious diseases in animals (foot-and-mouth disease, cattle-plague, etc.).

In the USSR the kolkhoz market no longer plays the role which cattle markets played earlier, but nevertheless the mass accumulation of animals and contact of humans from various population centers doubtless conceal a certain danger with respect to spread of infection, and this must be taken into account.

The methods existing in the USSR for the supplying of cattle and animal material are different in principle from the methods practiced in foreign countries. The Soviet system of state and cooperative supplies permits the full realization of veterinary-sanitary control over them. However, the supply organizations themselves not infrequently violate veterinary-sanitary requirements established by veterinary legislation and thus may facilitate the spread of foot-and-mouth disease. (During the foot-and-mouth-disease epizootic in the Tatar ASSR in 1928--1929, about 100 percent of all centers owed their origin to suppliers. Amphiteatrov, "The Campaign Against the Foot-and-mouth-disease Epizootic in the Tatar ASSR". Izvest. Bakter. inst. veter. upravl. NKZ TASSR, t. III, vyp. 2, 1930.)

A considerable role as a source of the spread of foot-and-mouth disease is still played by cattle-trails, which are in need of

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very serious attention on the part of supply organizations and bodies which exercise veterinary surveillance over the movement of cattle along these trails.

According to a report of Glebov's, a considerable percentage of all points contaminated with foot-and-mouth disease in Ural Oblast in 1927--1928 were along cattle-trails, and also along a railroad line. Commerce in cattle was in this instance the almost exclusive source of communication of foot-and-mouth disease and its spread within the oblast. ("From the Experience of an Anti-foot-and-mouth-disease Campaign". Glebov.) (Vestn. Sovrem. veterin., No 13--14, 1929.)

Railroad and water transport is also a frequent cause of the communication of foot-and-mouth disease. When veterinary-sanitary inspection is not sufficiently rigorous sick animals, and also animals in the stage of incubation, can be loaded into freight-cars for shipment. This leads to the virus-contamination of the freight-cars, fodder, manure, implements used to care for stock, etc. Personnel who care for the animals in transit can carry the virus on foot-wear and clothing upon returning to their farms.

Cattle-unloading areas, if daily cleaning of manure and disinfection after each shipment of cattle are not carried out, can also be a source of the spread of foot-and-mouth disease.

Railroad and water transport have repeatedly been the cause of the communication of foot-and-mouth disease into regions where it had not been previously.

OTHER SOURCES OF THE SPREAD OF FOOT-AND-MOUTH DISEASE

The sources of infection and channels of spread of foot-and-

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mouth disease are extremely varied and have not been exhausted in the information given here. In literature on the subject several cases have been described, for example, of communication of foot-and-mouth disease with variolous lymph.

De Blieck and Janssen in Norway established the fact of the contamination of variolous lymph by foot-and-mouth disease virus, the lymph having been destined for inoculation of human beings against small-pox. In Hungary in 1917 there occurred repeated outbreaks of foot-and-mouth disease after pigs had been inoculated with variolous calf-lymph which had contained, so it turned out, foot-and-mouth-disease virus (Hutyra and Marek). Perveleacu in Rumania observed a case of infection of a sucking pig with foot-and-mouth disease after it had been inoculated with variolous lymph. This case of disease served as the cause of the appearance of a new center of foot-and-mouth disease.

In the US outbreaks of foot-and-mouth-disease epizootic in 1908 and 1922 were caused by virus-contaminated variolous lymph. In one case variolous lymph delivered from Japan proved to contain foot-and-mouth-disease virus. Mohler and Rosenau confirmed experimentally the presence of foot-and-mouth-disease virus in the lymph which had been used. Gildemeister and Gel'm consider it essential before using variolous lymph to test it first on cattle for contamination with foot-and-mouth disease virus.

In the US, in Chicago, an outbreak of foot-and-mouth-disease epizootic in 1905 was caused by inoculation with anti-plague serum which contained foot-and-mouth-disease virus (Hutyra and Marek).

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CHAPTER IX

THE STRUGGLE AGAINST FOOT-AND-MOUTH DISEASE

GENERAL METHODS OF STRUGGLE

In almost all countries of the world the struggle against foot-and-mouth disease, with a few exceptions, is waged with the aid of a system of strictest quarantine-isolation measures. In certain countries, especially in the US, the basic, and essentially the only, measure of struggle against foot-and-mouth-disease is acknowledged to be the ~~individual~~ slaughter of all sick animals and all animals suspected of foot-and-mouth-disease infection. However, this measure, which has thoroughly justified itself in the practical struggle against foot-and-mouth disease in the US, has proved unworkable in other countries.

The compulsory slaughter of sick animals and animals suspected of foot-and-mouth-disease infection is a very effective measure only in cases of the communication of foot-and-mouth disease into countries or even individual localities which are not contaminated with this disease ~~until~~ the disease has become widely spread. In countries of western Europe where there are static centers of foot-and-mouth disease this measure of struggle becomes ineffective and practically unworkable, since with permanent outbreaks of foot-and-mouth-disease epizootics it would be necessary to slaughter constantly a large number of pedigreed and high-producing cattle.

For the purpose of studying methods of the struggle against foot-and-mouth disease the American Commission visited, in 1925--1926,

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a whole series of European countries (France, Germany, England, Denmark, Sweden, Holland, Belgium, Austria, Hungary, Switzerland, and Italy) and finally reached the conclusion that the methods of struggle against foot-and-mouth disease applied in Europe do not have a great influence on the spread of foot-and-mouth disease. Evidently even the various methods of inoculation applied in these countries do not change the situation with respect to foot-and-mouth disease (Schoening).

An explanation of the insufficient effectiveness of the methods of struggle against foot-and-mouth disease applied in the countries of western Europe must be sought in the fact that successful struggle with this disease is possible only under conditions of the simultaneous coordinated execution in these countries of a complete set of anti-epizootic and prophylactic measures, put into practice under the supervision of state veterinary agencies and with the active participation of the population itself.

The execution of strict quarantine, veterinary-sanitary, and organized-farming measures, which have decisive significance for the liquidation of foot-and-mouth disease, very often encounters, in foreign countries, opposition on the part of the owners of the animals themselves, and also of various "cattle-dealers" and traders in the products of animal-raising.

For the purposes of the study of the effectiveness of contemporary methods of fighting foot-and-mouth disease Fluckiger collected data for the period 1925-1933 for 33 countries, and as a result of analysis of these data reached the conclusion that foot-and-mouth

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disease continued to remain at the same level over the course of this period.

In the countries of western Europe the position of the campaign against foot-and-mouth disease has not been altered by the extensive application of highly-immune, anti-foot-and-mouth-disease, pluriva-lent serum (of the Riems Institute), in which considerable hope had been placed at one time, and also by the introduction into practice over the past 6--8 years of aluminum-hydroxide serum. In the countries of western Europe foot-and-mouth disease continues to bring extremely great losses to the farm economy, at the same time disorganizing mar-kets, bazaars, and municipal supplies of the products of animal-raising.

In 1936--1939 the countries of western Europe (Italy, France, Switzerland, Germany, and others) were infested by a panzootic of foot-and-mouth disease, which spread also to Denmark and Sweden and stopped only at the shores of the Baltic Sea. (Foot-and-mouth disease had been communicated to western Europe with imported sheep brought from Morocco to France in the spring of 1937.) How great were the economic losses occasioned by foot-and-mouth disease may be seen from the example of Denmark, which is, as is known, a small country with intensive cattle-raising industry. At the beginning of the epizootic, in order to liquidate it with greatest speed, 25,000 animals were sub-jected to compulsory slaughter on farms afflicted with foot-and-mouth disease, but success in restraining the epizootic outbreak was not ob-tained. Later, 105,000 farms were invaded by foot-and-mouth disease. Following the curtailment of compulsory slaughter in November--December, 1938, the disease spread with a rapidity which, in Plum's opinion "has no precedent in the Danish history of foot-and-mouth-disease epizootics".

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The country underwent enormous damage, numbered in the millions of kroner.

The system of fighting foot-and-mouth disease which exists in foreign countries is based on the application of strict isolation and quarantining of farms contaminated with foot-and-mouth disease, with the simultaneous carrying-out of measures of specific prophylaxis. This system, as evident in the conclusions drawn by the American Commission and Fluckiger, has proved inadequate not only for the complete liquidation of foot-and-mouth disease, but also for the lowering of the overall development of the disease and the losses caused by sickness. In the countries of western Europe foot-and-mouth disease remains as before a static infection.

The fight against foot-and-mouth disease in foreign countries embodies extremely great difficulties, inasmuch as the carrying-out of strict isolation and quarantining of farms affected by foot-and-mouth disease are extremely "cramping" measures for the owners of the animals, not to mention the compulsory slaughter of high-valued producing and pedigreed animals.

The real cause of the inadequate effectiveness of anti-foot-and-mouth-disease measures under the conditions of the farm economy in foreign countries depends in considerable degree on the social character of this economy.

It is known that essentially similar measures against foot-and-mouth disease are applied in the USSR, but they provide us with completely different results from the standpoint of effectiveness.

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Finally, the putting into practice of the system itself of anti-foot-and-mouth-disease measures in our country not only does not meet resistance on the part of the population, but, on the contrary, the population participates actively in the liquidation of foot-and-mouth disease, proceeding from considerations of the safeguarding of communal and individual animal-husbandry.

Anti-foot-and-mouth-disease measures in the USSR, in distinction to measures carried out in foreign countries, are put into effect as complex measures which reflect the latest achievements of modern veterinary science with consideration of all the advantages of the system of our socialist economy.

However, in spite of considerable achievements, by comparison with many foreign countries, in the domain of the struggle against foot-and-mouth disease, in certain regions of our country this disease continues to remain a static infection, from which it could penetrate to localities not contaminated with the disease. There exist, naturally, other sources of the origin of foot-and-mouth disease (communication of foot-and-mouth disease together with imported cattle and animal raw materials, etc.), but our country's greatest danger is represented by unliquidated static centers of foot-and-mouth-disease infection. Therefore, in solving the problem of liquidating foot-and-mouth disease it is necessary above all to achieve the complete liquidation of static centers of foot-and-mouth disease, which are the basic sources of its occurrence and spread. At the same time it is necessary to concentrate attention on veterinary-sanitary safe-guarding of our borders and, particularly, [redacted] the security-quarantine belts must become impenetrable barriers against foot-and-mouth disease.

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Measures for the liquidation of epizootic outbreaks of foot-and-mouth disease of "communicated" nature are also very important, but they do not quite solve the basic problem of the liquidation of static centers of infection, which are a factor constantly threatening the penetration of foot-and-mouth disease to uncontaminated republics and oblasts. The liquidation of the static nature of foot-and-mouth disease involves very great material and economic expenditures for the execution of anti-foot-and-mouth-disease measures, and difficulties of purely organizational nature, but it is entirely possible to overcome these under the conditions of a socialist economy.

With modern and correct organization of anti-foot-and-mouth-disease measures, individual outbreaks resulting from "communicated" infection can be liquidated within the confines of one or several contaminated points. Naturally, with the expansion of the zone contaminated with foot-and-mouth disease the difficulties of liquidating the foot-and-mouth-disease epizootic grow, as do the associated losses to the economy and the expenditures of state agencies for the epizootic's liquidation.

The basic elements of the complex of anti-foot-and-mouth-disease measures are: (1) prophylactic measures, (2) quarantining of population centers contaminated with foot-and-mouth-disease (farms), (3) active and passive immunization, and (4) disinfection.

In widespread experience with the practical campaign against foot-and-mouth disease it has been proved that all elements of this complex of measures, taken together and carried out simultaneously with the necessary persistence, assure definite success in the liquidation of foot-and-mouth disease.

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Prophylaxis in the struggle against foot-and-mouth disease should be regarded as the basic link in the overall complex of measures. Upon the least threat of the communication of foot-and-mouth disease to a given territory, prophylactic measures should embrace in the first order all kolkhozes, sovkhozes, settlements, etc., which are situated in direct proximity to the contaminated population center.

On all farms located under the threat of communication of foot-and-mouth disease there should be established for the whole time of the epizootic a special prophylactic regime for the care and keeping of cattle, excluding the possibility of the penetration of foot-and-mouth disease to the farm. All contact between the uncontaminated and contaminated farms should be ended, or at least limited as much as possible and placed under the strict supervision of the farm's veterinary personnel. Admission of outsiders to buildings where there are animals susceptible to foot-and-mouth disease or admission to herds in pasturage should be prohibited.

Assembling and transportation of cattle, assembling and transportation of animal raw material, sale at markets and transportation of coarse fodders in the territory of threatened population centers should be limited as much as possible and placed under the strictest supervision of veterinary control.

In individual cases where quarantine-isolation measures do not guarantee the speedy localization of foot-and-mouth disease and liquidation within the confines of the primary contaminated point, all supply and movement of cattle should be forbidden in the territory of

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the zone threatened with foot-and-mouth disease; trade at markets in the products of animal-raising should be limited and placed under the strict supervision of veterinary control. In addition, in this connection there should be an intensification of veterinary control over milk and cream centers, slaughter houses, meat and cheese factories, and also stocks of animal raw material, leather factories, wool-processing institutions, etc. This, of course, does not exhaust all targets of veterinary action.

Prophylactic measures should always be carried out with a consideration of all the peculiarities of the given locality (population point, factory-manufacturing settlement, city, etc.) and should be based on governmental expedience in the carrying-out of various measures.

In population points contaminated with foot-and-mouth disease a system of compulsory measures (strictest quarantine-restrictive measures, specific disinfection, and also active and passive immunization) should be put into action. Correct application of these in conjunction with prophylactic measures makes it possible under our circumstances to liquidate an epizootic of foot-and-mouth disease rapidly and without especially large losses.

As an example of how it is necessary to organize and execute measures, the experiment with the liquidation of foot-and-mouth disease is the Churvash ASSR (1936) may be cited. Foot-and-mouth disease first penetrated the territory of the Chuvash ASSR at the Zagotskot cattle-centers near the railroad stations of Urmary and Kanash. Upon discovery of foot-and-mouth disease at the Kanash cattle-center all cattle susceptible to foot-and-mouth disease,

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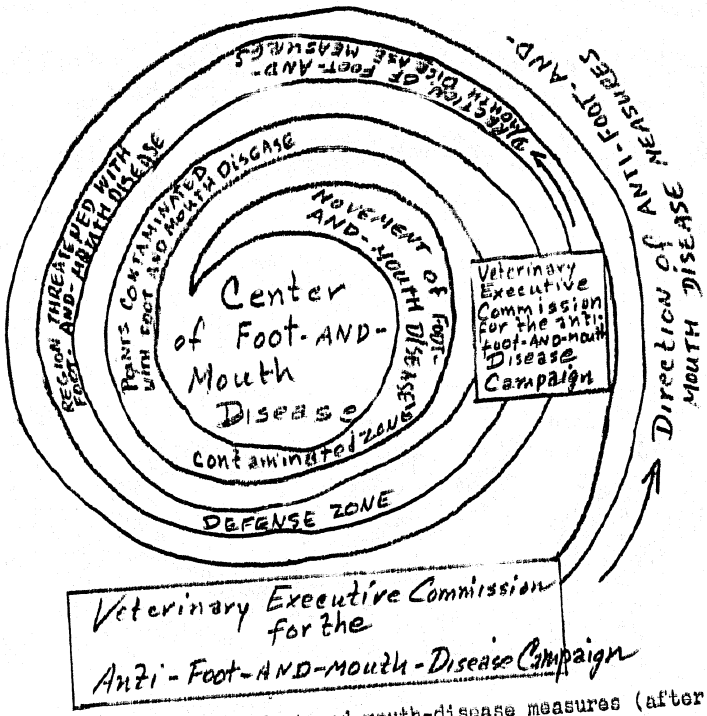
amounting to 202 head of large and 36 head of small cattle, were immediately killed for meat, and buildings were elaborately cleaned and subjected to disinfection. Thus the foot-and-mouth-disease center in Kanash was liquidated, and not a single further case of foot-and-mouth disease has been recorded in this rayon.

At the Urmary cattle-center, where there were only 16 head of large and 45 head of small cattle, the same measure of compulsory slaughter was carried out with some delay, when the infection had already succeeded in penetrating beyond the boundaries of the cattle-center, and therefore did not produce the same effect as in the first instance.



(Figure 24. Diagram of anti-foot-and-mouth-disease measures (after Amfiteatrov.)

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Foot-and-mouth disease spreads quickly, infesting four rayons in which 22 population points and 519 head of cattle were afflicted. However, even in this instance foot-and-mouth disease was very quickly liquidated with inconsiderable losses by means of strictest isolation of farms affected by foot-and-mouth disease and energetic execution of quarantine measures (complete prohibition for the population of travel from all these points, curtailment of all connections between the population of contaminated points and other population points, prohibition of postal delivery to individual addresses, prohibition of school-attendance on the part of students from contaminated farms, closing of churches during the epizootic, prohibition for workers from these points of travel to work at factories, establishment of 24-hour guard-posts around each contaminated population point, and finally, the extension of prophylactic quarantine to the whole region, and other measures).

This is not the only example from the USSR's experience in fighting foot-and-mouth disease where foot-and-mouth disease was liquidated quickly and without particular losses by decisive measures right up to the compulsory slaughter of sick animals and animals suspected of foot-and-mouth disease (Figure 24).

Compulsory slaughter as a method of dealing with foot-and-mouth disease cannot be recommended in all instances. However, it does not meet with protests on the part of farm organizations when it becomes necessary to handle fattened cattle or cattle exposed to "special treatment", inasmuch as foot-and-mouth-disease sickness involves a sharp decline in weight due to the rapid onset of emaciation, and not infrequently the death of fattened animals. Consequently, the basic

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measures on farms and in population points contaminated with foot-and mouth disease remain: quarantine, active and passive immunization, and disinfection.

QUARANTINING OF CONTAMINATED POINTS

Populationpoints (farms) contaminated with foot-and-mouth disease are regarded as most dangerous centers of infection, representing a threat to other farms which are not contaminated with respect to foot-and-mouth disease. Therefore, population points which are contaminated with foot-and-mouth disease, as a rule, are subjected to the most rigid quarantine. Quarantine consists of measures which are obligatory for all, which are directed to the speediest localization and liquidation of foot-and-mouth disease within the confines of the given contaminated point. The quarantining of contaminated points is a most important element in the complex of anti-foot-and-mouth disease measures.

Quarantine-restrictive measures achieve their goal only when they embrace all possible sources of infection, active (animals susceptible to foot-and-mouth disease) as well as passive (mechanical transmitters). The greatest danger is represented by animals which are sick or which have had foot-and-mouth disease. Therefore, there is strict prohibition of leading animals susceptible to foot-and-mouth disease outside the quarantine area before the removal of the quarantine, and with respect to animals which have had the disease, among whom there may prove to be virus-carriers, these restrictions are preserved for several months after removal of the quarantine. In the USSR restrictions with respect to animals which have had the disease

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are maintained for three months following the removal of quarantine, as far as their being taken to non-contaminated farms for working or breeding purposes, or for market-sale, is concerned. The expedience and effectiveness of this measure with respect to animals which have had the disease is justified by our extensive experience in Soviet practice. (In Switzerland animals which have had the disease, as possible virus-carriers, are assigned great significance in the spread of foot-and-mouth disease. Therefore, Swiss veterinary legislation does not authorize the taking of animals which have had the disease to uncontaminated farms or the placing of them in buildings with healthy animals which have not earlier had the disease, for a period of 6 months. Before the expiration of this period only killing of the animals in slaughter-houses is permitted, and they are transported in specially enclosed trucks.)

According to the conditions of the quarantine replenishment of a herd is forbidden, in order to avoid infection of newly-added animals.

The products of animal-raising can be a source of the spread of infection--meat, milk, and milk products. With compulsory slaughter the meat of sick animals can be used for food purposes on the farm itself, but with slaughtering at meat combines it is usually used in the preparation of cooked varieties of sausage and preserves. (Meat from sick animals killed with high temperature is considered conditionally fit for use. From Instructions for the Campaign Against Foot-and-mouth Disease, effective June 28, 1943.) Milk and milk products from farms under quarantine are authorized for use as food only following pasteurization for 30 minutes at 80 degrees centimeter or in the form of lactic-acid products. (Raw milk and milk products from cows of a

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contaminated group (herd) are not admitted as food for human beings or fodder for animals. Milk can be used or processed on the spot after boiling or pasteurization. Milk products (sour cream, curds, etc.) may also be prepared indirectly from raw milk with the authorization in each individual instance of a veterinarian attached to the farm. From Instructions for the Campaign Against Foot-and-mouth Disease, effective June 28, 1943.)

As a rule, shipment of milk or milk products for sale at markets is forbidden. In individual cases, with the authorization of veterinary and health bodies shipment of milk and milk products from suburban farms may be authorized, but only in pasteurized form or in the form of various milk products prepared from pasteurized milk.

Inasmuch as animal feeds from contaminated farms may serve likewise as a source of the spread of infection, shipment of them to other farms or for sale at markets is also not authorized. (Shipment of bulky fodders (hay, straw, etc.) is permitted only after removal of quarantine, but no earlier than 2 months after isolated storage of it in summertime and 6 months of storage of it in the remaining months of the year. Bulky feeds collected and stacked before the appearance of foot-and-mouth disease and not located in contact with animals sick with foot-and-mouth disease can be shipped after the removal of quarantine, and in individual instances earlier than the appointed interval, with the special authorization of the rayzemotdel. From Instructions for the Campaign Against Foot-and-mouth Disease, effective June 28, 1943.) Objects used in caring for stock when contaminated with foot-and-mouth disease may be a factor in the transmission of the infection. Therefore, all such objects (brushes, curry-combs, buckets, shovels,

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brooms, etc.) must remain in buildings for animals during the whole time of quarantine and must not be taken from them without thorough mechanical cleansing and specific disinfection.

It is essential to pay special attention to the people who care for sick animals. On collective farms and sovkhozes contaminated with foot-and-mouth disease the workers who take care of animals must be supplied with a change of clothing and foot-wear which they leave on the spot after work and do not take from the buildings without disinfection. Savel'yev, who has a number of times liquidated outbreaks of foot-and-mouth disease on large suburban farms, acknowledges the great significance of personal prophylaxis on the part of service personnel.

In liquidating foot-and-mouth disease on one of the leading pig-raising farms, according to Savel'yev's report, all personnel were rigidly confined to definite pig-raising areas. Arrival and departure from work took place under the observation of assigned veterinary personnel, foot-wear was subjected to compulsory disinfection, and overalls were changed daily. In addition, service personnel of uncontaminated and contaminated pig-farms were prohibited from any contact between each other in order to avoid communication of the infection to the uncontaminated pig-farms.

Observations from practice show that people who take care of sick animals or animals which have come in contact with them, for example, in connection with the provision of therapeutic treatment, are not infrequently culprits in the communication of foot-and-mouth disease to uncontaminated farms. Entry into buildings where there are sick animals should be authorized only for the people who care

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for them or who provide therapeutic treatment, with observation of necessary precautionary measures. All buildings where there are sick animals should be under constant guard in order not to admit to them persons not connected with their operation. Any exit from the contaminated farm for personnel connected with the care of animals should be authorized as an exception, and only with the consent of veterinary personnel responsible for supervising the execution of the quarantine. (In certain countries (Switzerland, Sweden, Germany, Hungary, and others) animal owners and their families are forbidden to leave their farms before the removal of quarantine in order to avoid the spread of infection.)

The so-called pasture quarantine is very often applied in the battle against foot-and-mouth disease in the summertime. If climatic conditions do not pose an obstacle, animals remain in the pasture during the entire period of sickness, in a section specially set aside and enclosed for those purposes. A special brigade of workers who must not be admitted to caring for healthy animals in other parts of the farm until complete recovery of the animals and removal of the quarantine, are set aside for the care of this herd. Pasteurization of the milk must be set up on the spot, and if this is impossible due to technical and economic conditions, then transportation of the milk to the place where pasteurization will be done is possible only in hermetically stoppered and sealed cans under the supervision of veterinary personnel. For each type of animal (cattle, sheep and goats, swine) it is necessary to set aside special pasture sections and keep the animals rigorously isolated in them until removal of quarantine.

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When quarantine is imposed on a population point all roads of common use which pass through this point are closed for the entire period of effectiveness of the quarantine. At all crossroads special identifying signs are set up and appropriate announcements and posters are hung up to serve as a warning. Special 24-hour guard-posts are established to survey access to the population point.

Quarantine must be imposed immediately upon discovery of the first cases of disease, before foot-and-mouth disease can spread further. The execution of quarantine-isolation measures must be carried out with all strictness, without any concessions and violations of the rules established by veterinary agencies. The fundamental idea of the imposition of quarantine on a farm or a whole population point is the localization of foot-and-mouth disease in a given center. This is possible only when quarantine and other measures are quickly extended and executed with full decisiveness.

It is necessary to strive for the liquidation of foot-and-mouth disease at the very beginning of its appearance, before it spreads to a large number of population points. Quarantine-restrictive measures become difficult to put into practice, particularly in periods of the population's most intense economic activity (spring sowing, grain harvest, etc.), when the disease has infested a large number of population points, and at times whole rayons.

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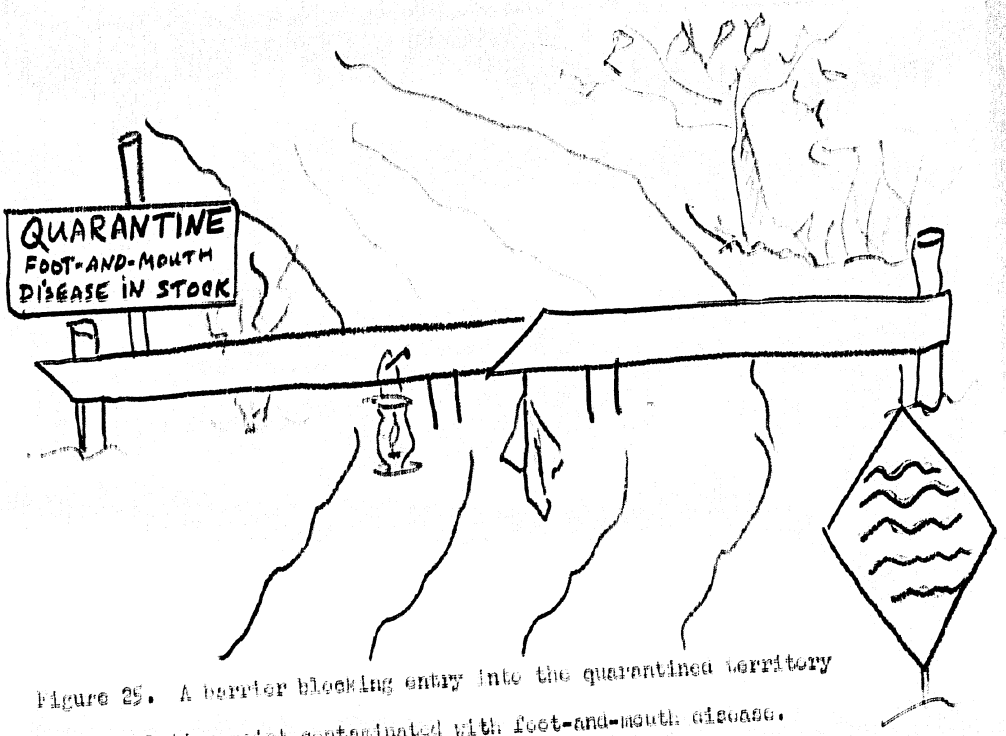

Figure 25. A barrier blocking entry into the quarantined territory of a population point contaminated with foot-and-mouth disease.

The duration of the quarantine always depends on how the population itself executes the measures prescribed by Instructions for the Campaign Against Foot-and-mouth Disease. Experience in fighting foot-and-mouth disease in the USSR shows that with correct organization of the campaign and persistent execution of it on the farm foot-and-mouth disease can be liquidated in the course of 6--8 weeks without exceptional losses. The quarantine is removed only following recovery of all animals or their compulsory slaughter for meat (swine), but no earlier than two weeks after the last instance of recovery of a sick animal. (In foreign countries the quarantine is removed in 14 days after the last instance of recovery of a sick animal (France and others), in 13 days, and in addition, restrictions with respect to taking animals to other farms or to the market for sale are kept for 14 days (Germany), in 30 days (Hungary). In Switzerland restrictions with respect to animal convalescents are maintained for 8 months.)

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Before removal of quarantine elaborate mechanical cleaning of buildings and objects used in the care of animals is performed to rid them of manure and dirt, and extensive specific disinfection is carried out also.

Numerous examples from Soviet practice demonstrate that with the execution of the full scope of quarantine-restrictive measures foot-and-mouth disease can be liquidated in a relatively short time within the confines of one or several points contaminated with foot-and-mouth disease.

Karimov reports that he succeeded in liquidating foot-and-mouth disease with the help of the most rigorous quarantine of the contaminated point. On all roads he set up 24-hour guard-posts, which were maintained right up to the end of the quarantine. Similar posts were established in settlements of the threatened area. Guards were appointed permanently in two reliefs. The stock were divided into groups according to individual types of animals and pasture quarantine was established for groups which remained in pasture. Foot-and-mouth disease was liquidated in 54 days. From the standpoint of material expenditures and the possible consequences caused by foot-and-mouth disease, all of these measures were very simple, inexpensive, and at the same time extremely effective.

A unique method of quarantining was applied by Yerko. In the village of Stel'makhovka he placed restrictions on a herd of cattle of 67 bulls, among which 5 head had been disclosed to have clinical symptoms of foot-and-mouth disease in veterinary inspection. Since the village had no building to keep the cattle, and there were no

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other suitable places for detention of the cattle for the period of quarantine, he placed the cattle right in the square in the center of the village itself. Each animal was tethered to a picket pounded into the earth. The whole area was "fenced in" with rope and warning signs were put up: "Cattle Sick with Foot-and-mouth Disease--Do not Approach". Feed and water were brought up with horses. The surface of the earth where the cattle were standing was flooded with 2 percent solution of creolin from a fire hose. (Creolin possesses no virucidal effect with respect to foot-and-mouth disease virus and application of it in this instance was completely futile.) Attendants washed their hands and feet with a creolin solution. The herd stayed in the village of Stel'makhova for 30 days, after which it was sent elsewhere. The village of Stel'makhova, basically devoted to animal-husbandry, consisting of 379 animal buildings and sheds, remained free of foot-and-mouth disease. In spite of the quite favorable outcome of the quarantining of sick animals applied by Yerko in the village square, such a risky measure cannot be recommended. Quarantining of cattle in the absence of the appropriate buildings can be accepted only in the pasture, far from a population point, on a completely isolated pasture and where there is a separate watering-place.

Quarantining for one-and-a-half to two months is a very burdensome measure, not infrequently threatening disruption of the managerial programs of kolkhozes, sovkhozes, and subsidiary farms of industrial enterprises. Therefore, quarantine, that all-important measure of the fight against foot-and-mouth disease, must be used very skilfully and not turned into a weapon for the disruption of managerial programs. The population will fulfill all quarantine-restrictive requirements if it is assured that such a measure is of short duration and economically expedient.

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Quarantining can give extremely effective results, but only when all measures connected with its execution are carried out thoroughly, precisely, rapidly, and decisively. In this respect the experience in liquidating foot-and-mouth disease in the Chuvash ASSR, which we cited somewhat earlier, is worthy of imitation.

In the USSR one of the causes of the spread of foot-and-mouth disease is the violation on the part of administrative and commercial-supply organizations of the quarantine-restrictive measures established by veterinary agencies.

ISOLATION OF SICK ANIMALS

With infectious disease individual and group isolation of sick animals is applied.

By means of individual isolation of sick animals, although even at the very beginning stage of disease, it is almost never possible to arrest the further spread of foot-and-mouth disease within the contaminated farm.

On pig-raising farms, where pigs are kept in separate pens, it is not possible to halt the spread of foot-and-mouth disease even with strict, timely isolation of whole pens of pigs which have exhibited the disease.

On one large dairy farm Savel'yev attempted to halt the spread of foot-and-mouth-disease on the farm by means of picking out clinically sick animals at the very beginning stage, with subsequent isolation of them. In spite of the very good discipline among staff

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personnel, foot-and-mouth disease gradually penetrated from one animal building to another, the development of the disease by animals was extended, and he was finally forced to resort to artificial infection of all remaining adult cattle unaffected by foot-and-mouth disease with virus-formole. All new-born young were inoculated with convalescent serum with a subsequent securing of passive immunity with chloroform vaccine and formol vaccine.

The liquidation of foot-and-mouth disease on large animal-raising farms, as shown by Savel'yev's experiment, is possible only by the method of strict isolation of the whole contaminated group of cattle and the keeping in strict isolation of all remaining animals, with the simultaneous administration on the farm of the complex of veterinary-sanitary measures. The method of individual isolation can have practical significance upon discovery of the first cases of foot-and-mouth disease on farms where cattle are kept by individuals, if they are kept separate from the common herd. In this case definite results may be obtained and further spread of the disease may be halted.

With Savel'yev, we succeeded on one of the suburban farms, during an outbreak of foot-and-mouth disease among cattle, in liquidating the disease within the confines of one cattle barn and in keeping it from another barn which stood near-by (at a distance of 120 meters) by means of strict isolation of the barn where the sick cattle were located and of the simultaneous carrying-out of all other veterinary-sanitary measures. On a suburban pig-fattening farm my associates and I, with the help of strict isolation of one contaminated pig-pen, prevented penetration of foot-and-mouth disease to all remaining pig-pens.

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On a large pig-fattening farm Savel'yev, Baranovskiy, Goldobenkov, and Volkova liquidated foot-and-mouth disease in 6 weeks, with the help of strict isolation of contaminated and uncontaminated pig-pens and the simultaneous administration of the complex of veterinary-sanitary measures. In this case, as a result of the measures administered by them 11 pig- ens out of 19 remained uncontaminated right up to removal of quarantine, in spite of the fact that the distance between pig-pens was only 33 meters in all. In carrying out the measures great attention was also paid to personal prophylaxis of staff personnel.

Practical observations show that if a sick animal has been in direct contact with other susceptible animals for some time the method of individual isolation almost never succeeds in arresting the spread of foot-and-mouth disease within the farm. Foot-and-mouth disease can be liquidated successfully without spreading to any other uncontaminated groups of cattle by the method of strict isolation of the whole contaminated group. Individual isolation can be used only as a method of prophylaxis with respect to high-producing, pedigreed, and other animals of special economic value.

The provision of strict isolation of groups of animals invaded by foot-and-mouth disease does not exempt the farm from the administration of the whole complex of measures envisaged by Instruction for the Campaign Against Foot-and-mouth Disease, nor from the imposition of quarantine on the farm.

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COMPULSORY SLAUGHTER

In the veterinary legislation of the USSR the compulsory slaughter of sick animals and animals suspected of infection, as a measure in the campaign against this disease, is not envisaged. However, in individual cases compulsory slaughter may prove to a measure which is very effective and economically expedient. It may be applied, for example, on large pig-fattening farms in order to avoid heavy losses in weight and mortality of pigs due to foot-and-mouth disease sickness.

Compulsory slaughter can be used successfully when foot-and-mouth disease appears in various cattle-centers and places for the temporary detention of cattle, inasmuch as the latter in the final analysis are destined for slaughtering for meat. With the help of compulsory slaughter foot-and-mouth disease was liquidated successfully at the Zagotskot cattle-center in Kanash (Chuvash ASSR), which was indicated earlier.

Compulsory slaughter cannot be applied with respect to pedigreed and high-producing animals. For purposes of the speedy liquidation of foot-and-mouth disease compulsory slaughter of animals must be accompanied simultaneously by all other measures directed toward the complete elimination of the infection on the territory of the farm.

Compulsory slaughter of animals as a measure in the struggle against foot-and-mouth disease applied at the very beginning of its appearance is acceptable only as an extreme, forced measure, with the authorization of the appropriate agencies, inasmuch as it is not envisaged in veterinary legislation.

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Among foreign countries, compulsory slaughtering is applied in the US and England. However, it has been repeatedly necessary to refrain from slaughter, since it would otherwise be necessary to liquidate a large number of high-valued pedigreed and producing cattle. In other foreign countries (Switzerland, Denmark, Sweden, etc.) compulsory slaughter is applied only

Figure 26. Truck for transportation of cattle sick with foot-and-mouth disease to a meat combine abattoir for slaughter, in Switzerland (after Burgi).

at the very beginning of an epizootic, when there is assurance than the outbreak of epizootic can be liquidated rapidly in this manner, without heavy losses to the animal-raising economy of the country (Figure 26). Many countries of western Europe (Belgium, Holland, Germany, etc.) have renounced this method of fighting foot-and-mouth disease entirely, inasmuch as the disease is brought in continually from neighboring countries.

In the US compulsory slaughter of all sick animals and animals suspected of foot-and-mouth-disease infection is considered the only reliable, the effective, and the cheapest measure for the liquidation of an epizootic.

Usually all cattle susceptible to foot-and-mouth disease of a contaminated farm are subjected to slaughtering, and also all cattle from farms which have been exposed to the danger of infection. The carcasses of compulsorily killed animals are buried, with their hides, in the ground, or burned. In compensation for the animals

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which have been killed, the owners are paid from 80 percent to 100 percent of the value by the state. American investigators consider that only through slaughter has it been possible to liquidate outbreaks of foot-and-mouth disease in the US with such relative rapidity. American investigators adopt a skeptical attitude to all other methods of fighting foot-and-mouth disease applied in western Europe. In foreign countries there are very many investigators and practical workers who are inclined to over-evaluate the significance of compulsory slaughter as a method of fighting foot-and-mouth disease (Burgi, Fluckiger, the American Commission, and others).

Burgi holds that in foot-and-mouth disease the same methods of campaigning are needed which were applied earlier with respect to cattle-plague. Compulsory slaughter he considers unconditionally the most rational and efficient method of fighting foot-and-mouth disease. Leclainche also has called repeatedly for the most severe measures of fighting foot-and-mouth disease. "In many cases," he says, "it would be much more advantageous and useful to give up the prolonged, minor, and difficult struggle with the infectious base; it must be exterminated immediately and at the root". (According to records of the XIIth International Veterinary Congress, held in New York in 1934).

At the XIIth International Veterinary Congress Fluckiger presented extremely convincing evidence in behalf of the contention that the correct application of compulsory slaughter in the combat against foot-and-mouth disease could have enormous practical significance. He insisted on a method of individual slaughter not only of all sick animals and animals suspected of foot-and-mouth-disease infection, but

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also on the slaughter of animals which had had foot-and-mouth disease (convalescents). He proposed two possible methods of slaughter: (a) individual slaughtering of all animals and destruction of their carcasses and (b) the slaughtering of all sick animals and animals suspected of infection with subsequent use of the meat, definite precautionary measures being observed.

The proposal advance by Fluckiger at the Congress for the introduction into practice of the method of compulsory slaughter as a measure of combatting foot-and-mouth disease encountered general approval and was adopted unanimously.

At a meeting of the 12th session of the International Epizootic Bureau in Paris (1936) Fluckiger again came out, in a special report, stubbornly in defense of slaughtering as the most reasonable method of fighting foot-and-mouth disease. As a result of consideration of the statements advanced by Fluckiger the following resolution was passed: "In view of the present state of our knowledge of foot-and-mouth disease individual slaughter of all sick animals and animals suspected of infection should be regarded as the only effective measure of fighting foot-and-mouth disease. This combat measure must be applied under any conditions, as prevident of the best results. Slaughter of all sick animals and suspected animals must be accompanied by mandatory disinfection and complete closing of all buildings on the farm in which the foot-and-mouth-disease virus may be preserved."

All these proposals of Fluckiger are nothing new in the field of combat against foot-and-mouth disease, but they still remain unexecuted, for the overwhelming majority of countries, due to the colossal spread of foot-and-mouth disease on the continent of western

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Europe, and also the eastern and, especially, the colonial countries.

INOCULATION WITH FOOT-AND-MOUTH-DISEASE VIRUS

Quarantine-restrictive measures always reflect heavily on the entire productive activity of the farm. The economic loss which they impose on the farm is sometimes greater than losses resulting directly from foot-and-mouth disease (lowering of production in milk cows, reduction in weight of fattened animals, various complications due to the development of foot-and-mouth disease, mortality in milk-fed young, etc.). Therefore, all measures must be organized so that foot-and-mouth disease is liquidated rapidly, without losses, and so that quarantine is removed from the farm in the shortest time.

In the USSR, in connection with the fact that at present there are not yet approved methods of active immunization (vaccination) for combatting foot-and-mouth disease, inoculations (artificial infection) with natural foot-and-mouth-disease virus are authorized to be carried out in contaminated areas. With the help of these inoculations a very rapid simultaneous and relatively mild development of the disease in animals is accomplished, (with simultaneous artificial infection of animals it is possible to prevent intensification of the virulence of the foot-and-mouth-disease virus, which may occur through passage of it in highly-sensitive animals in the initial period of appearance and spread of foot-and-mouth disease on the farm) which offers an opportunity to abbreviate considerably the period of quarantine imposed on the farm.

Inasmuch as inoculations are made with natural foot-and-mouth-

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disease virus, and the animals in consequence of having developed the disease become a source of dissemination of the virus in a certain time, the inoculations are applied with definite limitations. Inoculations are authorized for administration only to adult cattle under the condition of normalignant cases of infection. Inoculations should not be administered to high-valued pedigreed and producing animals, and also to young animals less than two months in age, due to their high sensitivity to foot-and-mouth disease. Nor is the administration of inoculations of natural foot-and-mouth-disease virus to all other susceptible types of animals (swine, sheep, goats, etc.) authorized, since complications which are difficult to treat are possible in consequence of such inoculations. All animals who have not been inoculated with virus and who are susceptible to foot-and-mouth disease should be subjected to strict prophylactic isolation and kept completely separate from the contaminated herd for the entire period, until all restrictions are removed from the farm.

From the standpoint of the danger which they represent, inoculated animals in principle differ in no way from animals which have developed the disease naturally. Therefore, all quarantine-restrictive measures are extended to them just as to animals which have been naturally infected, independently of the degree of clinical manifestation of the disease. Inoculations in cattle should be regarded as an extreme, enforced measure, inasmuch as there are no other safe and effective methods of active immunization. Administration of inoculations can be justified only when the whole complex of quarantine-restrictive is carried out on the farm in full scope and with utmost strictness.

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Inoculations of virus for the purpose of causing a milder development of foot-and-mouth disease in animals are a very old method. (In the countries of western Europe, with few exceptions (Hungary and others), inoculations of virus have long been renounced as a means of abbreviating the length of the course of an epizootic. Instead, the compulsory measure of slaughter of sick animals and animals suspected of infection is applied rather widely, and as a protective inoculation the serum of convalescents, and in recent years aluminum-hydroxide vaccine, are used.)

However, with the passage of time the technique of the inoculations itself has changed. In addition, instead of the saliva of sick animals which was used for inoculations earlier, virus taken directly from the aphthae themselves, where it is contained in very high concentration, has begun to be used. The fundamental inadequacy of old methods of inoculation was that they were administered with material of unknown virus-content, and the technique of the inoculations itself was extremely primitive.

Waldmann, and also Skomorokhov, proposed a new method of artificial infection. The essence of this method is that the virus, taken from fresh aphthae which have not ruptured or aphthae which have just ruptured, is applied to the surface of the mucous membrane of the upper lip, which has first been scarified. This method has been tested here in the Union for very extensive material and has obtained a thoroughly satisfactory rating on the part of investigators as well as veterinary doctors and practical workers.

According to data of Skomorokhov and Blazhevich obtained as the

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result of observations over the course of many years, with artificial infection administered with observation of all requirements the disease comes to nearly all animals which are susceptible to foot-and-mouth disease in the course of the first two or three days. In Vlazhevich's experiments, in one case of artificial infection of cattle 96.2 percent developed the disease in two days, and in another case 100 percent did so.

Lavrovskiy tested this method of inoculations on 92,700 head of cattle. According to his data, an average of 95 percent development of the disease was recorded on the 3rd to 4th day following the moment of infection. "The method of artificial infection by means of applying the virus to the scarified surface of the membrane of the upper lip, first introduced in our practice by Skomorokhov, must be recognized as the only method of artificial infection which is correct and provides the best results". (Lipatov. "Methods of Artificial Infection. Foot-and-mouth Disease in the Light of Modern Knowledge." 1932, pp. 115-119.)

Slavgorodskiy tested the method of virus-inoculations on 7249 head and came to the conclusion that "mass, vigorous development of the disease sets in, and quarantine can be removed in three weeks". Positive testimonials to the method of virus-inoculations by means of applying it to the scarified surface of the membrane of the upper lip may be found in the reports of many other veterinarians (Amfiteatrov, Polivanov, Kaymakov, Yenikeyev, Dol'shakov, Sorokin, Alekseyev, and others).

The technique of inoculations for the purpose of artificial infection is rather simple.

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(In the supplement to Instructions for the Campaign Against Foot-and-mouth Disease, effective 1943, there is a special "Exhortation to the Application of Foot-and-mouth-disease Virus Inoculations in Cattle", which is to be used.) Virus for inoculations is collected on the farm from sick animals who have developed the infection naturally, in the form of the epithelium of the walls of aphthae and the contents of fresh, unruptured or just ruptured aphthae. The collected material is weighed, cut into small pieces with scissors, and ground in a porcelain mortar with the gradual addition of a physiological solution of sodium chloride or cold boiled water (in the proportion of 0.5-1.0 gram of material to 500 cubic centimeters of liquid). The inoculant material prepared in this way is applied with a soft toothbrush or something else to the surface of the membrane of the upper lip, which has been scarified in preliminary.

For scarification of the mucous membrane the inoculative scarificator of Skomorokhov or the inoculative lancet of Waldmann may be applied (Figure 27), or finally, it is possible to make slight pricks in the mucous membrane with an ordinary needle from a syringe. Forty-eight hours after inoculations a control examination of the animals is made in order to verify the activity of the virus. Development of primary aphthae on the site of application of the virus can serve as an indication of this activity (inoculability of the virus).

(Figure 27. The inoculative scarificator constructed by Professor Skomorokhov.)

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The application of natural virus in the practice of combatting foot-and-mouth disease often meets with serious objections, inasmuch as artificially infected animals sometimes develop the disease just as severely those which are infected naturally. Searching for more complete and safer methods of inoculation of the foot-and-mouth-disease virus, some authors recommend the application of virus-formole for the same purpose.

Savel'yev added a solution of formalin 1:1500 (in the proportion of 1 part of virus-emulsion to 1.0 parts of solution) to the foot-and-mouth-disease emulsion instead of the physiological solution or cold boiled water, and afterward left the prepared virus for 24 hours at room temperature. Applying virus-formole the author succeeded in "weakening the course of the foot-and-mouth-disease epizootic on the farm". Fedotov also used virus-formole for artificial infection during an epizootic and concludes that "in animals treated with virus-formole there were fewer complications than in those which had developed the disease naturally, they felt better, their appetites were preserved, and aphthae were fewer and quick to heal". However, the author refrains from final conclusions.

This method of artificial infection with virus-formole has been tried by many veterinarians, who are also inclined to give preference to it before the usual method of artificial infection.

It seems to us that there is insufficient foundation for referring to any special advantages of the application of virus-formole since it can at best cause protraction of the incubation period (which is extremely undesirable), but it is impossible to prevent

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subsequent generalization of the infection by this means. Thus, the severity of the infection itself does not depend only on the properties of the virus at the moment of its application to sensitive tissues. Foot-and-mouth-disease virus which has first been attenuated, developing in the form of primary aphthae, regains its virulent properties and after a certain period of incubation causes generalization of the infection.

This problem cannot be considered solved decisively until the conclusions made by individual authors are confirmed experimentally.

Terent'yev, coming out in defense of the method of inoculation with foot-and-mouth-disease virus, was completely in the right that natural development of the disease by animals not only does not reduce the danger of accumulation of the virus on the contaminated farm, but creates an immeasurably great danger with respect to the spread of foot-and-mouth disease to other susceptible animals within the farm as well as beyond its boundaries.

The development of protracted cases of the disease by animals is extremely undesirable from the epizootological point-of-view.

Proper application of the method of inoculation of natural virus in cattle, within the complex of all other veterinary-sanitary measures, can prove to be a very useful means of the rapid liquidation of foot-and-mouth disease on a contaminated farm.

THE DEDYULIN METHOD OF INOCULATION

The method of virus-inoculations proposed by Dedyulin is known

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in our literature under the designation of the "accelerated method of combatting foot-and-mouth disease in infected herds". The method proposed by the author is, as will be seen further on, essentially a modification of the method of artificial infection. The essence of this method is that the virus, used in the form of saliva from sick animals, was applied not to the mucous membrane of the oral cavity, but to the skin of the inner surface of the otic shell, scarified in preliminary.

Dedyulin considered that "virus applied here should enter promptly into reaction with susceptible cells, and consequently the process of development of antibodies should begin rapidly. Vaccinal substances form rapidly on the site of inoculation and do not give the virus, which is penetrating into the organism from the site of inoculation, an opportunity to multiply, since vaccinal substances originating from the site of inoculation alter the medium of the organism in a direction unfavorable to the microbe". Inoculated animals should, according to Dedyulin's statement, develop the disease mildly, without a visible clinical picture. This method at one time received very wide dissemination among practical workers, and was applied with varying success and without any criticism for 15 years. It had partisans not only in the ranks of numerous practical workers (Burgimov, Belobrzhitskiy, Kartsev, Moshalov, Lisitsyn, Sokolov, and others), but also among a certain group of scholars (Mikhin, Romanovich, Ispolatov, and others).

This method was first subjected to experimental study by Skomorokhov, then by Blazhevich, and finally, by a special commission composed of Skomorokhov, Blazhevich, Romanovich, and others. As a

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result it was established that "upon inoculation into the skin of the ear one portion of the animals inevitably becomes sick with subsequent generalization of the infection and all clinical symptoms of foot-and-mouth disease, and the other portion remains clinically healthy following inoculation, but then it does not acquire anti-foot-and-mouth-disease immunity". Consequently, Dedyulin's method can be recommended for protective purposes nor for the purpose of artificial infection, and must be abandoned as not possessing any practical significance. These conclusions have found complete confirmation in the subsequent experimental investigations of other authors and the observations of many practical workers. (However, long before Dedyulin's method there was known in Russia an old Kalmyk method of fighting foot-and-mouth disease, consisting in the passing through the ear of a thread which had been moistened with saliva from sick animals, this method in principle differing in no way from Dedyulin's method. The same thing was done at one time by Clerc, who did not obtain convincing proof in favor of this method. Lehwess and Braudess applied the virus to the otic shell by means of knife-pricks, but this method likewise did not obtain application in practice.)

In Southern Rhodesia during the 1932 foot-and-mouth-disease epizootic intranasal inoculations were used, by means of spraying the virus onto the mucous membrane of the nasal cavity. They seemingly gave completely satisfactory results. However, these inoculations also do not differ at all in principle from other methods of artificial infection.

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INOCULATIONS OF BLOOD AND SICK-ANIMAL SERUM

For purposes of causing a mild non-malignant course of the infection with forced inoculations many investigators have used blood or sick-animal serum.

The French investigators (Roux, Vallee, Carre, and Nocard) recommended stubbornly at one time the application of serum containing the virus, after preliminary seasoning of it in a refrigerator for a month. To obtain the serum the authors recommended taking blood from cattle artificially infected for this purpose, in the period of greatest rise in temperature (i.e., in the period of generalization of infection). Inoculation of such a serum in the amount of 1.0 cubic centimeters causes, according to the assertion of the authors, a mild development of the disease in animals and the formation of a stable and prolonged immunity (up to 6 months).

For the same purpose Cosco and Aguzzi injected cattle with the blood of sick animals. Such inoculation usually did not produce the clinical picture of the disease in animals, apart from mild fever reaction, and at the same time caused the formation of a stable and prolonged immunity. Moussu recommended injecting 50--20 cubic centimeters of blood taken from sick animals, with the addition of 1 percent sodium citrate. Inoculated with citrated blood, cattle develops foot-and-mouth disease very mildly without any complications, according to the author's statement.

Blood and serum have also been applied in various modifications by many other investigators (Rousseau, Lutrario, Johann, etc.), beginning with the time of Kitt (1896), who first applied blood of

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sick animals for the purpose of active immunization. Numerous observations of another kind are also known, where as the result of application of blood or serum the animals developed the disease very severely with all clinical symptoms of sickness and various complications.

Consequently, these methods of forced inoculations do not possess any advantages over the application of the virus on the scarified surface of the membrane of the oral cavity.

Valee and Carre applied blood of convalescents in the amount of 1.0 cubic-centimeter to 1 kilogram of live weight, with simultaneous (or no later than 5 days) injection of 1.0--10 cubic-centimeters of virulent blood ("simultaneous inoculations"). Animals thus inoculated, according to the authors' statement, develop the disease without visible clinical symptoms and acquire a sufficiently stable immunity.

DISINFECTION IN FOOT-AND-MOUTH DISEASE

Disinfection is a most important component element in the overall complex of anti-foot-and-mouth-disease measures. Above all, it has great significance in the period of liquidation of foot-and-mouth disease on the farm. The application of constant (daily) disinfection provides an opportunity, if not to eradicate thoroughly, at least to reduce substantially the amount of virus given off by sick animals into the surrounding medium. This, in turn reduces the danger for other animals which are threatened by infection, and there is also a reduction of the degree of danger of the spread of foot-and-mouth disease on the territory of the farm itself as well as beyond its boundaries.

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Still greater significance from the standpoint of the conclusive liquidation of foot-and-mouth disease on the farm is possessed by the final disinfection which is carried out before removal of quarantine following the complete recovery of all animals. Through final disinfection, which is always preceded by elaborate mechanical cleaning to rid all buildings of manure and dirt, complete elimination of all sources of infection in the animals' surroundings is obtained.

Disinfection should also be used as widely as possible as a means of foot-and-mouth-disease prophylaxis. First, such prophylactic disinfection should be performed on farms situated in the territory of the threatened zone. Prophylactic disinfection should be performed in all places where animals congregate (live-stock shows, stops along cattle-trails, railroads, etc.) upon the slightest danger of the communication of foot-and-mouth disease from localities which during the course of the previous year have been contaminated with foot-and-mouth disease. In many countries very great importance is attributed to such disinfection (Denmark, Switzerland, Sweden, Germany, etc.).

Certain difficulties in the widespread use of disinfection as one of the most important methods of combatting foot-and-mouth disease arise due to the extremely limited assortment of specific methods applied for foot-and-mouth-disease disinfection. There are in all only several chemical preparations which have been recommended by science and tested in practice (caustic alkali and formalin), and these are rather inefficient and expensive preparations.

The various disinfectants used in practice to combat bacterial

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infections (corrosive sublimate, phenol, creolin, sulpho-carbolic compound, soap-creosol solution, etc.) are ineffective with respect to the foot-and-mouth-disease virus. It was pointed out earlier that the virus is not killed for 22 days in a 5 percent solution of creolin, and for 5 months in a 1 percent solution of carbolic acid.

In Minett's experiments, the virus, even after 3 hour exposure to phenol and creosol solutions, did not lose its activity. In carcasses buried with lime the virus remained visible as long as in carcasses buried without lime (English Commission). Unslaked lime (CaO), usually used in the form of 25--30 percent suspension in water (milk of lime), (with the addition of water to unslaked lime slaked lime is obtained--calcium hydroxide--$CaO+H_2O=Ca(OH)_2$.) does not kill the virus (the American Commission, Trautwein, Waldmann, Magnusson, and others).

Of all disinfection methods used in practice for combatting infectious diseases, only caustic soda and potash and formalin can be recommended for disinfection in foot-and-mouth disease.

On the basis of its experiments the American Commission (1927) reached the conclusion that caustic soda in concentration of 1 and 2 percent kills the virus in the course of one minute, and even in concentration of 0.25--0.50 percent under the same conditions, in the course of 3 minutes. The virucidal effect of caustic soda solutions has been tested in the presence of manure, urine, and earth, i.e. in conditions close to those encountered in practice. The experiments performed by the same commission to test the practical value of caustic soda under pasture conditions confirmed thoroughly the virucidal effect of caustic soda with respect to the virus. Incidentally, the American Commission also studied the possibility of replacing

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caustic soda with a 5 percent solution of anhydrous sodium carbonate, but negative results were obtained.

Linett, who studied the virucidal properties of caustic soda, generally obtained similar results. In concentrations of 0.25--0.50 percent caustic soda did not kill the virus in one minute, but always in three minutes. In concentrations of 1 and 2 percent caustic soda in all cases killed the virus in 1--3 minutes.

The English Commission on foot-and-mouth disease does not deny the good disinfectant action of caustic soda, but considers it poorly adapted to practical application. Solutions of caustic soda rapidly lose their virucidal properties in the presence of organic and inorganic substances, and also from the action of the air. (According to Avramenko's data, the quantity of caustic soda in a 5 percent solution of caustic soda left open for 24 hours is reduced to 1.8 percent. In the open air caustic soda reacts with carbonic acid and is converted into soda.) Moreover, in the concentrations used for disinfection caustic soda has a harmful, irritant effect on the outer surfaces of animals and the skin of man. In his experiments, Lignieres confirmed the high effectiveness of caustic soda as a disinfectant with respect to the virus. In Lignieres' experiments a 1 percent solution of caustic soda killed the virus in one minute.

Trautwein and Reppin (1928), under experimental conditions, studied the virucidal action of caustic soda and caustic potash and came to the conclusion that a 1 percent solution of these substances kills the virus in 5 to 10 minutes. Winkel holds that caustic soda and sulphuric acid are good disinfectants for foot-and-mouth disease. In his experiments, a 1--2 percent solution of caustic soda very rapidly

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killed the virus. In a solution of sulphuric acid of the same concentration the virus, on the other hand, survived considerably longer. In a solution of caustic soda, the virus in the form of exudate ("lymph") dies 60 times faster than in a solution of sulphuric acid of the same concentration.

Soviet investigators have also engaged in the study of the virucidal properties of caustic soda, and have obtained somewhat different results.

In the experiments of Koeltsina and Ovsyannikov, which they performed in the Foot-and-mouth-disease Institute, a 1 percent solution of caustic soda did not kill the virus for 2 hours in the epithelium of aphthae, and a 2 percent solution of caustic soda killed it only in the course of 30 minutes. Almost the same results were obtained by Khomenko. In her experiments a 2 percent solution of caustic soda did not kill the virus for 30 minutes, but considerably attenuated its virulence. In the same author's experiments, the virus lost its virulence completely in 30 minutes in 2 and 3 percent solutions of caustic soda.

In studying the virucidal properties of caustic potash with respect to the virus, Ratner and Tonigs established that in 5 percent concentration the latter loses its virulence in 30 minutes. For testing the virucidal action of caustic potash the virus was taken in the form of the walls (epithelium) of primary aphthae of a guinea pig. The authors feel it possible to recommend caustic potash as a specific disinfectant in the absence of other, stronger-acting disinfectants (formalin, caustic soda). The mechanism of caustic potash' action on the virus is evidently the same as that of caustic potash.

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(Gatner and Tonigs explain the effectiveness of the virucidal action of caustic soda with respect to the foot-and-mouth disease virus by the fact that caustic soda, as a strongly acting base, causes a rapid process of hydrolysis and dissociation into components of the albuminal substance with which the virus is connected. Having lost its "protective coating" in consequence of the process of hydrolysis, the virus is easily exposed to the reaction of the active group of hydroxyl ions, whereupon a medium with ph 11 is created. In this medium unfavorable to survival, the virus loses its activity, i.e. loses its virulence.)

For disinfection Minett stubbornly recommends formalin in the form of a 1 percent solution which, according to his data, acts considerably better in the presence of an organic substance than caustic soda, and its virucidal action can last at least for 24 hours. He considers formalin the most effective preparation for disinfection. Trautwein and Keppin, on the other hand, consider formalin less advantageous for practical purposes, since formalin acts slowly (1 percent solution of formalin kills the virus in 6 hours) and compares in the strength of its virucidal effect with unslaked lime, chloride of lime, creosol water, etc. Waldmann, and also Trautwein and Keppin, consider a quite essential shortcoming of formalin its strongly irritant effect. It is known that even weak concentrations of formalin cause irritation of the mucous membranes of the eyes and respiratory tracts in human beings as well as animals.

Problems of foot-and-mouth-disease disinfection were also discussed at the XIth International Veterinary Congress at London, in the reports of Andrewes, Waldmann, and Lignieres.

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Heldmann recommended using caustic soda in the form of a 2 percent solution for the disinfection of buildings and implements used in caring for animals, and in the form of a 1 percent solution for disinfection of the outer surfaces of animals. (In disinfecting the outer surfaces of animals with 1 percent solution of caustic soda it is necessary to observe definite caution, since even weak solutions of caustic alkali possess a rather strong burning action.) In France caustic alkali are used for disinfection of the outer surfaces of animals and hoofs in the form of 0.4 percent solution, which in this concentration is completely harmless.

Ligniéres, in turn, declared at the Congress that "of all known chemical compounds the most effective is caustic soda, even in very weak concentrations".

The International Veterinary Congress recognized that the most effective methods of disinfection in foot-and-mouth disease should be considered to be: (a) physical methods--steam under pressure or boiling water, and sunshine and (b) chemical methods--formalin and alkaline preparations (NaOH and KOH).

Caustic alkali and formalin, as is known, are used in industry and agriculture, and often are inefficient methods. Some investigators have undertaken the quest of new, more easily obtainable, and cheaper methods of foot-and-mouth-disease disinfection. Rushits (Kazakhstan) has suggested using ash-alkali solutions as a substitute for caustic alkali. On the basis of tests which he performed he has come to the conclusion that ash-alkali solutions prepared from haloxylon, birch, and straw ashes in 25 percent concentration, and also fir ashes in

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10 percent solution, kill virus from the epithelium of aphthae in 2 hour exposure. He recommends using solutions of haloxylon, birch, and straw ashes for foot-and-mouth-disease disinfection in the form of 20 percent concentration and solutions of fir ash in the form of 10 percent concentration.

Sulpholiquid B. S. (a preparation of sulphuric acid), which received rather wide usage in its time in the practice of combatting foot-and-mouth disease in Germany, is almost unused at the present time, since its virucidal action is disputed by some investigators, and in addition this preparation is very costly and hard to obtain. (From Waldmann's report at the XIth International Veterinary Congress in London in 1930.)

Trautwein established that sulphur gas (SO_2) possesses adequately defined virucidal properties and can be used for practical foot-and-mouth-disease disinfection. Steidle studied the virucidal action of various preparations containing SO_2 and came to the conclusion that gas disinfection with SO_2 could have practical significance. Incidentally, all preparations which he tested were more active in small concentrations than in stronger ones.

On one of the leading svinosovkhozes in the USSR an experiment was performed in disinfection with chlorine gas which, according to Kolesnikov, gave completely satisfactory results.

For disinfection of buildings Soshestvenskiy recommends the method of chlorination (Soshestvenskiy, N. A. "A Course in the Pharmacology and Pharmacotherapy of Domestic Animals." Part II, 1931, page 169.) or the use for the same purpose of chlorine-water. In his

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opinion, "large-scale use of chlorine-water can be made for the systematic combatting of foot-and-mouth disease". He somewhat overestimates the significance of chlorine-water in this case, and thus far there are no serious foundations for such a broad recommendation of chlorine-water as a specific method for foot-and-mouth-disease disinfection.

In testing the virucidal properties of a sulphur-creosol mixture Trautwein, and also Glitsky, obtained negative results. Helm and Weesemann, in their experiments with 3 percent solution of sulphur-creosol mixture, on the other hand, obtained completely satisfactory results (the foot-and-mouth-disease virus died in one minute). Sais studied the virucidal action of soap-creosol mixture, of solutions of citric and hydrochloric acid, obtaining conflicting results. In Sais' experiments the virus remained active for 24 hours in a 2 percent solution of soap-creosol mixture.

In Switzerland the use of unslaked lime in the form of a 25 percent suspension (milk of lime) is accepted for foot-and-mouth-disease disinfection.

In the US, according to instructions for combatting foot-and-mouth disease, the use of chloride of lime (calcium chloride) is accepted for disinfection in the open air of sheds, pens and the surface of the earth. For disinfection of closed buildings a solution of "dosophane" (a complicated mixture with crystalline carbolic acid) is used, and for living and storage buildings, dairy structures, etc., formaldehyde vapors are used.

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German veterinary legislation, according to Trautwein's report, authorizes the use of the following disinfectants for foot-and-mouth-disease disinfection: unslaked lime (5--30 percent), creosol water (6 percent), sulphur-carbolic mixture (3 percent), corrosive sublimate (0.1 percent), carbolic acid (3 percent), and formalin (1 percent), although all these measures, with the exception of formalin have a weakly virucidal effect with respect to the virus.

Prussian veterinary legislation prescribed the use only of solutions of caustic soda for foot-and-mouth-disease disinfection. For the disinfection of buildings (walls, floors) and objects used in caring for animals the use of 1 percent solution of caustic soda with 5 percent addition of lime was recommended. (From a circular of the Prussian Ministry of State Properties and Forests of October, 1937.) In carrying out disinfection during frosts it was recommended, in addition, that sodium chloride be added to the prepared solution of caustic soda (in the proportion of 0.5--1.0 kilograms of sodium chloride for each 10 liters of solution).

In France the use of a solution of caustic alkalis (caustic soda) is recommended for foot-and-mouth-disease disinfection. (From Instructions for the Use of Caustic Soda for Foot-and-mouth-disease Infection, of March 23, 1933, Paris.) For disinfection of cattle buildings--walls, stalls, ceilings, floors, sewer troughs, etc., and also for litter, solutions of caustic soda in proportion 8:1000 are used, and for disinfection of the outer surfaces and hoofs, and the hands and clothing of personnel who care for animals a proportion of 4:1000 is used. For every 100 square-meter area use of no less than 100 liters of disinfectant solution is recommended. Lime may also be added to the

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basic disinfectant solution.

In the US the disinfection of hay and straw suspected to have been soiled with virus by sick animals, according to existing instructions, is performed by means of removal of the upper layer (1½--2 feet) and burning. For disinfection of hay Minett recommends using 0.1--1 percent solution of formalin, which in such dilution has no harmful effect, either on the nutritious or the gustatory qualities of hay. In the US, according to the same instructions, disinfection of hay is performed with a 1 percent solution of formalin.

In silage, as shown by Belogorskiy's and Lipatov's experiments, the foot-and-mouth-disease virus perishes quickly. In cases where there is a large amount of fodder suspected of contamination with virus, it may be used for the preparation of silage.

The disinfection of salted hides is best performed by the method which Belogorskiy developed under our guidance. For this, salted hides are soaked in a brine solution with the addition to it of 0.1--2.0 percent caustic soda, or 0.5 percent bisulphite or 5 percent solution of soda ash. The brine solution is used in four-fold proportion to the material being disinfected (for 100 kilograms of material 400 liters of disinfectant solution of disinfectant brine must be used), and disinfection is performed at a temperature of 15--20 degrees centimeter. Disinfection of leather goods by this method has absolutely no effect on the quality of the leather.

In American instructions (1915) there is an indication that hides taken from compulsorily killed animals must be soaked in a solution of one part mercuric chloride and 100 parts of sodium-chloride

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solution for 4 hours (sodium-chloride concentration no less than 15 percent). (In the US this instruction has lost significance, inasmuch as compulsory slaughter of sick animals is executed without subsequent usage of the meat and hides.)

Constant disinfection of buildings where there are animals sick with foot-and-mouth-disease should be performed daily. Final disinfection, then, is as a rule performed before removal of quarantine based on recovery of all sick animals.

Buildings are subjected to disinfection, and also objects used in caring for animals. Moreover, the outer surfaces of animals are treated with disinfectant methods by means of rubbing-down with brushes dipped in disinfectant solution. Hoofs are also cleaned, and scraped. Final disinfection must of necessity be preceded by elaborate mechanical cleaning of all buildings, feeding troughs, and objects used in caring for animals.

During liquidation of foot-and-mouth disease on one large pig-raising farm Savel'yev and associates carried out continual disinfection daily in contaminated pig-pens. In all remaining pig-pens threatened with infection prophylactic disinfection of buildings and objects used in caring for stock was performed every 5 days, and in addition each animal was subjected to supplemental sanitary treatment by being driven through special baths filled with formalin solution. In this way the author succeeded in arresting the spread of foot-and-mouth disease on the farm.

For cleaning and washing of buildings and utensils Dobson recommends using hot solutions (50--60 degrees centimeter) of ordinary

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washing soda. He obtained good results with the use of 1 to 4 percent solution of soda.

Disinfection of walls and ceilings can be performed at the same time through white-washing.

The disinfectant solution is used in the proportion of 1 liter of solution of the disinfectant liquid to 1 square-meter of floor surface. Aside from mechanical cleaning and disinfection of buildings, objects used in caring for animals and various farming devices, clothing of those who care for stock and of veterinary personnel, the most elaborate cleaning of the whole territory of the farm or of the entire population point must be carried out.

For disinfection of the clothing and foot-wear of persons who are in contact with sick animals or other sources of infection, it is recommended that formalin be used. Where gas-chambers are available fumigation with sulphur-dioxide gas may be used for the same purpose. Boiling and wet or dry steam can also be used for the disinfection of foot-wear and clothing.

In Switzerland, corrosive sublimate, together with formalin, is used for the disinfection of clothing. The various objects

Figure 28. A special costume used in performing disinfection.

used in caring for animals can be treated according to the properties of such objects: with formalin, caustic soda, boiling water, hot steam, chlorine gas, sulphur-dioxide fumigation, etc. Various vehicles and carts can be treated in the same manner. In American

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instructions on combatting foot-and-mouth disease it is recommended that the wheels of carts be coated with slaked lime. For disinfecting objects used in caring for animals, and also vehicles and carts, the same methods may be used which are used in general for foot-and-mouth-disease disinfection (caustic soda, caustic potash, formalin). Preliminary mechanical cleaning and washing of them with hot solutions of ordinary washing soda should be regarded as a very important condition of reliable disinfection.

In some foreign countries, certain further restrictions are applied following final disinfection with respect to buildings where there have been animals sick with foot-and-mouth disease.

In Switzerland newly acquired animals which are susceptible to foot-and-mouth disease can be placed in buildings where there have been sick animals no sooner than 30 days after the performance of elaborate mechanical cleaning to rid them of manure and dirt, and specific disinfection.

In the US the same periods of restriction with respect to buildings where there have been sick animals are applied. In addition, buildings are first checked for the presence of the virus by means of placing animals susceptible to foot-and-mouth disease in them for some length of time. Even after such a test it is recommended that farmers place their stock in such buildings gradually and in small groups.

In many foreign countries (Switzerland, Sweden, Denmark, and others) special state disinfection squads have been organized, fitted with all essentials for the performance of disinfection (Figure 28).

In the USSR also, disinfection squads have been organized in

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a number of oblasts.

Disinfection is worthwhile only when it is performed with specific methods and covers all sources of infection.

DISINFECTION OF MANURE

Manure and the washings of manure, and also the sewage liquids of slaughtering enterprises, can play a very serious role in the spread of foot-and-mouth disease when they are soiled with the virus. Practical observations, and also experimental research, show that the virus can be preserved under certain conditions for a prolonged period in manure, manure-water, and sewage liquids, and can cause outbreaks of foot-and-mouth disease among susceptible animals.

Under the conditions of Central Asia, manure is a basic source of the spread of foot-and-mouth disease, according to a statement by Kindygkov.

Therefore, the question of disinfection of manure and manure-water, and also the sewage liquids of slaughtering enterprises, has great practical significance.

The simplest method of infection of manure is the stacking of it in heaps for burning.

Kocked at one time recommended stacking manure and litter used by sick animals in heaps and covering them on top with horse manure (35--50 centimeters). Under such conditions manure is self-disinfected, according to his assertion, and in 8 days can be taken out to the fields for improvement of the soil.

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Wagener performed a whole series of experimental investigations on the study of the viability of foot-and-mouth disease in manure and proposed a more complete method of disinfecting the manure. He recommends piling it in heaps 1.25 meters high and 1.5--2 meters wide (on the surface of the earth). Where manure is piled for disinfection the ground should first be covered with dry straw, dry peat, or uninfected dry manure in a layer 25 centimeters thick. Following this the manure to be disinfected is piled up. At the top the manure pile is covered with a layer of dry straw 10 centimeters thick and then all this is sprinkled with a layer of sand also 10 centimeters thick. (Professor Gelitser, in his article on "Disinfection of Manure" (Veterin.praktika, No 12, 1929) gives, among other things, a complete untrue explanation of the biological processes under whose influence disinfection of manure takes place. He considers that "the spontaneous warming and decomposition of manure takes place due to the development of microbes without the admission of air".

Decomposition in manure is always an aerobic-anaerobic process, the highest temperature, up to 70 degrees, occurring only in the first stage of decomposition of the manure with free aeration. This stage, with vigorous development of thermophilic bacteria, continues about 2 weeks in all. With a surface temperature (that of the air) of 21 degrees the temperature in a well-aerated manure pile reaches 67.5 degrees in the first week of storage. Under anaerobic conditions the decomposition of the manure usually occurs more slowly, in consequence of the formation of various organic acids which restrain the development of microbes. Under anaerobic conditions the temperature usually does not exceed 7 degrees (Khudyakov, "Agricultural Microbiology", 1926, page 269-270).) Straw, dry manure, and peat are used in this

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in this instance as poor conductors of heat, the sand for protection of the straw from external deposits.

Through the use of large-grained sand sufficient porosity of the top-sprinkled layer is created, which is essential for aeration of the manure. With such a method of piling manure complete disinfection of it takes place, and in 3 weeks it can be considered completely safe for soil-improvement or other purposes.

In his original experiments Wagener established that the virus in the form of the epithelium of the walls of aphthae in a normal manure pile, at a depth of 15 centimeters, died in 7 days; at a depth of 25 centimeters under the same conditions in 24 hours; at a depth of 50 centimeters, under somewhat different conditions, in 6 to 9 hours; at a depth of 50 centimeters, under somewhat different conditions, in 6 to 9 hours; while, on the surface of the manure pile it kept its viability up to 26 days. This led Wagener to the idea of creating conditions for the process of burning manure which would make it possible to achieve a maximum temperature capable of destroying the virus.

When the manure is piled in heaps according to Wagener's method the temperature inside the manure heap may exceed 65--70 degrees centimeter, its increase taking place first in the upper layers of the manure pile, and then the processes of decomposition spread inward, where high temperature is noted considerably later. Corresponding to the development of the processes of decay of the manure the virus, too, dies first in the upper layers of the manure piles, and then in deeper layers.

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The method of disinfecting manure in foot-and-mouth disease proposed by Wagener is technically very simple, easily executable under any farming conditions, and at the same time is the most reliable.

Interesting research on the disinfection of manure was carried out by Kindyakov. He established that under wintertime conditions, in frozen manure piled in heaps for disinfection the processes of decomposition do not take place until the onset of warm weather.

Increase in temperature in manure piles begins on the 6th to 9th day following the warming of the outer air, beginning in the upper layers of manure and reaching the deepest layers only on the 24th day. Maximum temperature is noted first in the upper layers of the manure piles (58--60 degrees centimeter); in the lower layers--100 to 125 centimeters deep--it is no higher than 42--52 degrees centimeter. Kindyakov established that in manure piles heaped up in early spring the processes of decomposition set it considerably earlier, but depend greatly on the temperature of the outer air. In such cases the virus dies in 33 days.

In wintertime under the conditions of Kazakhstan the foot-and-mouth-disease virus in manure can be preserved for 156--168 days, or in other words, all winter and into the first two months of spring.

Consequently, manure piled into manure heaps in wintertime, fall, and early spring can be used for farming purposes no earlier than a month following the onset of warm spring weather (when the around-the-clock temperature is higher than 0 degrees centimeter). Manure which is not taken to the manure pile in warm weather, according to the same author's data, must be piled in manure heaps for

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biothermic disinfection and use for farming purposes in an elapsed time of 40 days.

On every well-run farm a manure deposit should be set up remotely from animal buildings at a distance of not less than 200 meters, where manure, litter, and food remnants polluted with foot-and-mouth-disease virus should be taken for biothermic disinfection.

Studying methods of disinfection of manure-water Wagener established a definite dependency between the duration of survival of the virus and the amount of ammonia contained in the sewage canals of animal sheds and drains. (Accumulation of ammonia in manure-water takes place in the process of decomposition of urine. Urea decomposes into ammonia and carbonic-acid gas according to the following formula: $CO(NH_2)_2+H_2O=2NH_3+CO_2$.) It turned out that in manure-water in open sewage canals the virus remained viable for 39 days. Ammonia content in this case was only 0.2 percent, with the hydrogen-ion concentration pH 5.6. In manure-water which was carried off in closed sewage canals the virus remained viable for 14 days, the ammonia content was 3.1 percent, and the concentration of hydrogen ions was pH 7.4. In another instance, with the same system of closed sewage canals, the virus died in manure-water in the course of only 16 hours, with ammonia content 3.2 percent and hydrogen-ion concentration pH 8.4.

The same dependency of the survival of the virus was established for manure-water in sewage holes. In sewage-collection drain-pits which manure-water enters through an open system of sewage canals the virus can survive for 39 days. In sewage pits which the manure-water enters through closed sewage canals it died in 9 days, with ammonia

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content of 0.64 percent. Consequently, from the standpoint of disinfection of manure-water, the system of closed sewage canals must be recognized as one of the best. (The requirements of hygiene and prophylaxis in infectious disease where animals are kept in stalls are met best of all by cattle sheds with a well-arranged system of manure-disposal and closed sewage canals for removal of manure-water.)

There is no less significance in the disinfection of the sewage waters of slaughtering enterprises which receive animals sick with foot-and-mouth disease for compulsory slaughter, and also of various enterprises occupied with the working of animal material.

As a result of experimental research Wagener established that the virus can be preserved from 14 to 140 days in sewage waters, depending on various conditions (temperature of the out-of-doors, water-temperature, the effect of biological and mechanical factors, bacteriophages, etc.). In studying the influence of out-door temperature on the duration of survival of the virus in sewage waters he came to the conclusion that low temperatures inhibit the development in them of biological processes, which in turn facilitates more prolonged survival of the virus. In fall, with out-door temperature from 13--18 degrees centimeter the virus remained viable 40 to 49 days; in winter, with temperature from 4 to 13 degrees up to 103 days; while in summer, with temperature from 17 to 21 degrees centimeter it died in only 14 to 21 days.

Consequently, the sewage waters of various enterprises which deal with the processing of animal products and material should, before they leave the confines of the enterprise, expose them to

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preliminary disinfection or conduct them through a closed canal-system into special fields fertilized to sewage which are not accessible to animals susceptible to foot-and-mouth disease.

The use of manure and manure-water for soil improvement on the territory of the contaminated point itself (kolkhoz, sovkhoz, subsidiary farms) is completely safe and possible in summertime when the soil is to be tilled immediately and deeply, but this all should be done under the strict supervision of veterinary personnel.

VETERINARY-SANITARY RESTRICTIONS WITH RESPECT TO THE PRODUCTS OF ANIMAL-HUSBANDRY

The products of animal-husbandry have always played a very great role as sources of infection in the epizootology of foot-and-mouth disease. Particularly dangerous in this respect is the meat of compulsorily killed sick animals and animals suspected of foot-and-mouth disease, and also milk from sick animals when it has been obtained from them at the very beginning stage of development of the disease.

In the meat of animals killed at the stage of generalization of the infection (in the period of fever-state, the virus can be discovered in all organs and tissues. Storage and transportation of meat is accomplished, as is known, at low temperatures (cold-storage, ice-cars). At low temperature the virus is preserved and can exist for a long time in frozen meat without losing its activity in the process.

It must also be considered that sodium chloride, in practical use by industrial enterprises which process the products of animal-husbandry, also preserves the virus and facilitates its more prolonged survival.

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In quick-chilled and frozen carcasses the virus can keep its viability up to 145--149 days (English Commission on foot-and-mouth disease). According to early data of Nocard, Gins, and also Krause, virulent blood kept cold, stayed virulent up to 5 months. Repeated freezing and thawing in the range from --18 to +18 degrees centimeter does not kill the virus. It perishes only when the meat is warmed up completely (under the action of temperature of 10--12 degrees centimeter for 24 hours), due to the influence of an accumulation of lactic acid (Schlegel, English Commission on foot-and-mouth Disease, and others).

The meat of sick animals and animals suspected of foot-and-mouth disease which have been killed with high body-temperature cannot be accepted for market-sale without preliminary disinfection.

In meat combines and slaughter-houses the meat of compulsorily killed animals, killed in connection with foot-and-mouth disease, should be processed into meat preserves and cooked varieties of sausage, and cannot be approved for sale to the population in raw form, even as a provisionally suitable product.

The meat of animals killed in the recovery-stage with normal temperature represents no danger after the meat-carcass has been heated for an established time (12--24 hours), as it is completely sterile with respect to the virus. Such meat can be approved for shipment, with certain restrictions, as provisionally fit.

Parts of the animal organism attacked by foot-and-mouth disease --the head (tongue), extremities, udder, stomach--doubtless represent a danger and should be disinfected at the site of killing by means of

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cooking for one hour at 100 degrees centimeter, and the bones should be cooked at the same temperature for 2--2.5 hours. However, disinfection of individual organs of compulsorily killed animals by means of cooking impairs their nutritious value and taste qualities.

Doronin has suggested a new, more rational method of disinfection of organs attacked by foot-and-mouth disease, particularly of the tongues--smoke-curing, to be specific. He has done special research to determine the possibility of using this method with a consideration of technological treatment of meat products before they are smoked.

It was established that the virus dies in only 14 days in the process of salting itself in consequence of a gradual changing of its reaction in the direction of acidity (up to pH 5.4 in pickled form and ph 5.3 in extract). In smoking the tongues were disinfected in 16 to 18 hours. Consequently, the method of hot-smoking is completely reliable and can find application for a more rational use of the meat and meat products of animals sick with foot-and-mouth disease.

Various by-products of slaughtering enterprises, particularly blood, are very often used for fattening of swine on large suburban pig-fattening farms. Like all collected blood it can be used in feeding stock only after preliminary disinfection. According to early data of Loeffler and Frosch, and also Zemann, virulent foot-and-mouth disease blood can be disinfected only at 60 degrees centimeter for 5--15 minutes. At lower temperatures more prolonged intervals are necessary for disinfection. According to the data of Traum and Schoening at 37 degrees centimeter virulent blood is disinfected only in 24 hours and at 42 degrees centimeter in 12 hours. The use of blood from

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slaughtering enterprises as feed for animals in raw or insufficiently disinfected form involves the danger of spreading foot-and-mouth disease.

Giving stomachs and other by-products of slaughtering enterprises to swine as feed can be accepted only after it has been tested on the territory of the enterprise itself and shipped in disinfected form.

In large butchering enterprises certain organs of animals killed for meat are used to obtain various preparations (endocrines, etc.). The need has arisen for studying methods of disinfecting them.

In the English Commission's experiments with disinfection of small pieces of the thymus gland containing virus, by means of cooking, it was established that the water in which the meat is placed must be brought to a boil, and after this must be cooked continually for not less than 5 minutes in order to kill the virus conclusively.

When large (320 grams and more) of thymus gland were used for experiment this interval proved insufficient for killing the virus.

In milk and milk products the virus, depending on various conditions of storage and processing, can remain viable for a very long time. In all countries definite restrictions are applied with respect to the use of milk for feeding human and animals. It is known that the virus dies upon the boiling and souring of milk. Therefore, milk from foot-and-mouth-disease-contaminated farms must be pasteurized or boiled before being used for feeding humans or animals (calves, sucking-pigs, etc.).

According to Iensen, in the pasteurization of milk (70 degrees centimeter) the virus dies in 10 minutes; (according to Instructions

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for the Campaign Against Foot-and-mouth Disease, affirmed by the Chief Veterinary Administration of the NKZ SSSR in 1943, raw milk and raw milk products from cows of a contaminated group (herd) are not acceptable for feeding humans or animals. Milk from such animals can be used or processed after boiling or pasteurization (at 80 degrees centimeter) for 30 minutes.) Weiss recommends warming milk to 90 degrees centimeter for prophylactic purposes. In Germany the pasteurization of milk by the usual methods for the purpose of disinfection with respect to the virus is recognized as inadequate. Shipment of such milk is authorized only after warming of it at 85 degrees centimeter for one minute, or at 70 degrees centimeter for 30 minutes.

Unsterilized milk, as a general rule, cannot be accepted for shipment beyond the limits of a contaminated point or used on the spot for feeding humans or animals. The sterilization of milk should be performed at the point of origin, i.e. on the farm itself, by means of boiling or pasteurization, or finally, it can be processed for lactic-acid products. It is also possible to prepare milk products from milk or cream which has been boiled in preliminary.

Cheese prepared from milk does not represent a danger for man, since the virus dies in the process of preparation of the cheese itself: partially under the influence of warming, but mainly under the influence of the prolonged action of acid or ripening of the cheese. However, Ostertag considers that only cheese from milk heated at 81 degrees centimeter for 1 minute can be used for food.

The effecting of the most rigid veterinary supervision on all enterprises, without exception, where processing of the products of animal-husbandry takes place (meat combines, milk and cheese factories),

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and veterinary surveillance over the use and utilization of the various by-products resulting from such processing are most important conditions of the improvement of our country's sanitary position with respect to foot-and-mouth disease.

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CHAPTER X

THE PROBLEM OF IMMUNITY

IMMUNITY

Immunity to foot-and-mouth disease, which occurs in consequence of the interaction of the causal agent of the infection and the animal's system, is nowadays disputed by no one. However, certain questions related to immunity remain as before unclarified and in need of a more fundamentally scientific illumination.

Modern investigators point to the well-known singularity of foot-and-mouth-disease immunity, which differs in certain respects from bacterial immunity. It has been proved with respect to post-infection immunity for many virus-infections that this is intense and prolonged, sometimes extending over the whole course of an individual life (Zil'ber, Gardner, and others). The immunity occurring in animals following development of foot-and-mouth disease, as shown by experimental data and practical observations, which is also distinguished by considerable stability and intensity. For a determinate interval the animal's system becomes resistant to spontaneous or natural as well as to artificial infection (Vallee and Carre, Waldmann, Trautwein, Lignieres, and others).

In experiments with cattle, the English Commission established that animals which have had the disease acquire a resistance to foot-and-mouth disease which cannot be overcome by contact, and likewise experimental infection by means of intramuscular injection of virus. However, the English Commission succeeded in individual cases of artificial infection of animals via the membrane of the oral cavity in observing specific formations--small aphthae on the site of injec-

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tion of the virus. Such acquired resistance to foot-and-mouth disease following nature development of the disease usually continues over a range of one to two years. After this interval immunity gradually disappears, and the animals again become susceptible to foot-and-mouth disease (Vallee and Carre, Lignieres, and others).

In studying phenomena of immunity certain investigators have established that a tissue (local) immunity first develops, and then a humoral immunity (Terni). It is possible that this can be connected with intracellular parasitic development of the virus, which is generally typical for ultravirus infections. According to Nicolau, individual cells of the organism into which the virus has penetrated react actively against the causal agent. "They develop agglutins which transform the elemtary small-pox bodies or tiny rods of rabies and herpes into cohesive conglomerates (Guanieri, Negri bodies). In this process the cellular tissue immunity does not depend on antibodies circulating in the blood or on participation in the formation of its reticulo-endothelium." (Likhachev, N. V. "Immunity in Ultravirus Diseases." Veterinariya, No 11-12, 1945, pp. 14-17.)

It is well-known that convalescent-serum, and also hyperimmune serum, injected into an animal for prophylactic purposes does not protect it from the appearance of primary aphthae on the site of injection of the virus. It only prevents the development of generalization of the infection and, consequently, the appearance of secondary aphthae. This occurs in all cases, independently of the place and method of injection of the serum and of whether the serum is injected simultaneously with the virus or somewhat earlier, or, on the other hand, somewhat later.

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In a guinea pig which has had foot-and-mouth disease it is possible in 3 or 4 months to cause a new case of foot-and-mouth disease, but it is then limited to the appearance of only primary aphthae, and generalization of the infection does not set in.

All these facts gave Terni, in his day, a basis for introducing the concept of tissue and humoral immunity in foot-and-mouth disease. He states that in foot-and-mouth disease, just as in small-pox, a tissue immunity occurs first, and humoral immunity develops later.

Waldmann and Trautwein tested the hypothesis expressed by Terni as to two types of foot-and-mouth-disease immunity (tissue and humoral) and confirmed it experimentally. For this purpose they infected pigs, first intravenously and then in various intervals of time these same pigs were infected intracutaneously, in order to check the onset of tissue immunity. As a result of the experiments they established that in 48 hours after intravenous infection, intracutaneous injection of the virus no longer causes any specific changes on the site of injection, which indicates, consequently, the formation of tissue immunity.

In experiments on cattle, Waldmann and Trautwein established that tissue immunity disappears earlier than humoral immunity. When animals were infected artificially in the first 4 months following their development of foot-and-mouth disease these investigators always obtained negative results, and only in 6 to 7 months were individual cases of spontaneous infection established, but without subsequent generalization of infection (relative immunity).

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After 18 months such animals usually lose humoral immunity, too, and consequently, can again be infected and take sick with all the phenomena of natural foot-and-mouth disease, i.e. with the appearance of primary aphthae on the site of injection of the virus and of secondary ones resulting from generalization of the infection.

Krause injected the virus in guinea pigs intratesticularly, which was accompanied by unclear, barely discernible changes, and he establishes the presence of immunity in them.

Waldmann and Trautwein, in experiments on guinea pigs, proved that in the blood of infected animals specific antibodies can be observed only on the 7th day following infection, while tissue factors of immunity can be proved considerably earlier in them.

Stockmann and Minett called these phenomena of foot-and-mouth-disease immunity "complete" and "partial" immunity, since in their opinion all differences between the two types of immunity--tissue and humoral--are limited to the degree of intensity of immunity and do not at all represent a particular form or character of the latter. They declare that immunity to foot-and-mouth disease is based exclusively on the presence of specific antibodies in the blood, and therefore it is incorrect to refer to the existence of some special tissue or "cellular" immunity apart.

Stockmann and Minett succeeded, with intracutaneous injection of small amounts of virus, in transforming cellular-tissue, or partial, immunity into complete immunity.

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In the light of modern views as to immunity in infectious diseases, it would in our opinion be more correct to regard it with respect to foot-and-mouth disease not as two types of immunity (tissue and humoral), but as an immunity of the animal's system arising from tissue and humoral factors.

The very mechanism of formation of immunity in ultravirus infections, particularly in foot-and-mouth disease, has not yet been figured out by science. Levaditi, Alberta-Lorante, and Galloway consider, on the basis of study of the histogenesis of aphthae and of proceeding also from epitheliotropic localization of the latter, that immunization of epithelial and membranous cells occurs with the help of epithelial fibrils.

The question as to whether the intensity and duration of immunity depends on the prolonged or constant presence of virus in the system, also remains unstudied. It is possible that the virus in the associated (inactive) state survives for a long time in the animal's system following recovery, and makes the system non-susceptible to repeated infections of the same virus. (Zil'ber, L. A. and Lyubarskiy, V. A. "Immunity". Biomedgiz, 1937, pp. 292-304.) The intracellular nature of viruses, which in Rivers' opinion appears in the animal's system as a particularly intimate type of parasitism between the etiological basis and the cells of the host, also makes it incumbent to search for connections between the stability of immunity and the prolonged survival of the virus in the system.

In connection with this there naturally arises the very serious question as to whether sterile or unsterile (infectious, labile) occurs with foot-and-mouth disease. There are no direct experimental data

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for answering this question, but "anti-virus immunity is often infectious" (Zil'ber). It is possible that the stability and duration of immunity in ultravirus infections is based on the presence of virus in the system (Winkler). Incidentally, American investigators succeeded, with the aid of cataphoresis, in proving true, with a different infection) the presence of virus in the tissues of a system which was completely healthy but had had a case of disease several months before. It is possible that the infection transmitted by the system in such cases ends in symbiosis (Gardner and others).

J. Lignieres associates the stability and duration of immunity in foot-and-mouth disease directly with the antigenic properties of the virus. Specifically, in Lignieres' own experiments type O virus caused a more stable and prolonged immunity than type A virus. In J. Lignieres' opinion some viruses, independently of their type classification, likewise possess stronger antigenic properties, and others on the other hand have weaker ones. Consequently, it may be said that the "quality of immunity" depends on the "quality of the virus itself" (the antigen).

The question as to whether there exists a connection, and if so exactly what kind, between the virulence of the virus and its antigenic properties remains almost uninvestigated. In this respect Waldmann's experiments offer a certain interest; he attempted to weaken the virulence of the virus by means of prolonged cultivation of it in the presence of living tissues, for the purpose of preserving its antigenic properties and then using it for immunization. However, experiments showed that weakening of the virulence of the virus is paralleled by a decrease in its antigenic properties. In addition,

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immunity also depends, as is well-known, on the reacting capacity of the system itself.

The question as to the role enacted by the local reaction which takes place on the site of injection of the virus, in the form of a primary aphtha, in the formation of active immunity to foot-and-mouth disease has continued for a long time to remain the object of disagreements. These disagreements have arisen not only in connection with the manner in which the problem of active immunity should be solved, but also the question as to whether the appearance of local reaction is generally essential to the occurrence and development of immunity has remained clouded.

Vallee and Carre long declared that active immunity, occurring as the result of spontaneous development of foot-and-mouth disease, can be also caused through vaccination, but under the condition of the development -- however mild -- of the disease in the animal, and unfailingly with the appearance of one or several aphthae like those occurring with natural infection. As early as 1911 Vallee declared at one of the scientific conferences that "elaborately performed experiments on cattle and pigs have demonstrated that it is impossible to vaccinate animals against foot-and-mouth disease without simultaneously causing the formation of aphthae, even though only one, single aphtha is formed"....

De Blieck states that between the intensity of the reaction of the organism and the length of duration of immunity there is a direct relationship. When inoculations are simultaneous, the occurrence of a stable and prolonged immunity in animals susceptible to foot-and-

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mouth disease is likewise accompanied by the formation of aphthae on the site of injection of the virus (membrane of the oral cavity). For the occurrence of a stable and prolonged immunity, the formation of a local reaction is unconditionally necessary.

Waldmann, on the basis of his own investigations, considered that active immunization of cattle without the development of the disease with clinical symptoms of sickness is completely impossible. For the formation of immunity, in Waldmann's opinion, a reaction of the organism in the form of a mild, transient fever-state is necessary. However, more stable immunity can develop only with the development by the animal of the disease with the appearance of primary aphthae, or even generalization of the infection.

Toussieng and Fogedby, and also Frenkel and Van Vaveren in Holland, on the basis of their experiments on active immunization performed on cattle and pigs, came to the conclusion that the occurrence of immunity to foot-and-mouth disease is completely possible without the appearance of visible clinical phenomena.

In certain cases the injection of living virus in susceptible animals, in an amount insufficient for infection ("subinfectious doses"), causes a condition of complete immunity in them, this latter not differing in any way from the immunity which occurs following development of foot-and-mouth disease as the result of natural infection (Stockmann and Minett). However, these authors state by way of reservation that as a rule injection of living virus in amounts which do not cause natural development of the disease produces only partial (relative) immunity.

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The experiments of Soviet investigators, performed under practical conditions on tens of thousands of head and cattle, have demonstrated that the immunization of animals with virus inactivated through the use of chloroform or formalin causes in them a relatively stable and sufficiently lasting immunity, without the appearance of visible clinical symptoms of disease (Skomorokhov, Dubyanskiy and Khomenko, Lavrovskiy and Dobrotvorskaya, Kindyakov, Voronin and Zotova, Lavrovskiy, Rafalovich and Volkov, Yuskovets, Savel'yev, and others). However, the early statement remains valid, that only natural development of foot-and-mouth disease, accompanied by the clinical picture of the disease, can cause such a condition of immunity in the animal as not to be curtailed by the injection of even considerable amounts of virus. (Scientific discussion on the question of the role of local reaction in the occurrence of foot-and-mouth-disease immunity offers great historical interest at present, inasmuch as the very problem of active immunization for this disease can be considered completely solved at present.)

Individual instances, when animals, even after development of foot-and-mouth disease with the appearance on the site of injection of the virus of primary aphthae and generalization of the infection, did not acquire immunity to the same strain of virus, were observed by Waldmann. The cause of this somewhat unusual phenomenon is seen by him in the onset of "weakening of the foot-and-mouth-disease virus". In this instance, in our opinion, the cause was evidently not so much the weakening of the virus as a change in its immunogenic properties.

Many investigators (Terni, Vallee and Carre, and others) have repeatedly observed individual instances of "falling off of immunity"

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in foot-and-mouth disease, whose origin has not yet received suitable scientific explanation.

Termi described a special "anaphylactic" type of the disease, in which animals has developed foot-and-mouth disease were again infected and became sick with foot-and-mouth disease in a short interval of time.

J. Lignieres called this phenomenon "perturbations", which occur in the process of formation of immunity with repeated reinfections at short intervals. Vallee and Carre, in checking observations which they had made earlier, obtained these phenomena of "falling off of immunity" under experimental conditions by means of repeated injections of virus in experimental animals. As a result, they came to the conclusion that with frequent reinfections of animals which had developed foot-and-mouth disease, immunity becomes attenuated rather quickly, and they may then become diseased again, usually in more severe form than before. The question remains open as to whether there takes place here a unique "sensitivisation" of the organism to the virus-type of the same name.

According to data of Vallee and Carre, based on experimental study of immunity, and also on practical observations, acquired immunity to foot-and-mouth disease in cattle extends an average of no less than 12 months (265-450 days), and according to data of the American Commission no less than 210 days. J. Lignieres reached the conclusion, on the basis of his experiments, that immunity in cattle lasts an average of 12 months and never last more than 15 months. Gins and Weber determine the length of duration of immunity in cattle at 6--9 months. In the experiments of Stockmann and Minett, immunity in cattle lasted 13.5

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months, being tested by means of intramuscular injection of the virus. In experiments of these same authors, humoral immunity in a certain bull lasted 32 months, and with subsequent reinfection its duration increased to 52 months.

Manninger asserts that development of foot-and-mouth disease in cattle causes a condition of stable and intense immunity, which for a term of 5 months cannot be interrupted by injection of even very large amounts of virus. Osorov, on the basis of personal observations during the foot-and-mouth-disease epizootic in 1924-1926, came to the conclusion that in cattle immunity acquired due to natural infection lasts no less than 6 to 9 months, but no more than 14 months, following which animals can again develop foot-and-mouth disease.

In epizootological literature one encounters individual references, evidently based on practical observations, where immunity to foot-and-mouth disease following development of the disease in cattle lasted 3 to 5 years (Mazaini), 5 to 7 years (Aichorn), 7 years (Schwenk), 1 to 10 years (Aidamgrodskiy), 8 years (Arseni), 9 years (Schunck). In Kenya it was observed that animals which had had foot-and-mouth disease 3 years before did not develop it upon the outbreak of a new epizootic. However, a somewhat critical attitude must be adopted toward all these observations, inasmuch as they are in conflict with modern views on the duration of immunity to foot-and-mouth disease.

In swine, immunity acquired due to spontaneous development of foot-and-mouth disease lasts no longer than 10--11 months (English Commission).

In a guinea pig which had had foot-and-mouth disease the presence

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of immunity was proved over a term of 3 to 4 months, and even longer (Stockmann and Minett). According to Waldmann and Trautwein, complete immunity in the guinea pig lasts 3 months, and relative (partial) immunity 6 months. Gins described one case where immunity in the guinea pig lasted 307 days. Weber reports another case where immunity in the guinea pig, on the other hand, lasted only 1 month in all.

In contemporary literature on the subject there are almost no indications with respect to the time when immunity sets in, for natural as well as artificial infection. Weber reached the conclusion on the basis of his investigations that in the guinea pig it sets in 14 days following infection.

Waldmann and Trautwein proved the presence of antibodies in the blood of guinea pigs as early as the 7th day following infection.

Stockmann and Minett, on the basis of their investigations, reached the conclusion that injection in a guinea pig of virus killed with formalin (Under the reaction of weak concentrations of formalin the foot-and-mouth-disease virus evidently is not killed, and merely passes over into an inactive state, at the same time keeping its antigenic properties.) causes the setting in of immunity in only 4 days, this immunity lasting at least one month.

Intramuscular or subcutaneous injection of virus in the guinea pig does not always cause development of foot-and-mouth disease, but does not pass without leaving its mark on the development of immunity. If after this virus is applied to the guinea pig on the plantar surface of the rear extremities (following preliminary scarification), there then develops on the site of application a primary aphtha,

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without subsequent generalization of the infection. This indicates that with intramuscular or subcutaneous injection of virus there occurs the formation of only partial (relative) immunity.

A guinea pig vaccinated three times with a dose of virus treated with formalin (formole-antigen) acquires a more stable immunity than with the injection of a single dose of the same formole-antigen.

According to data of ours, obtained in experiments on cattle, immunity develops in individual animals, upon active immunization with virus attenuated short of complete inactivation, toward only the 4th day, and in the whole herd toward the 11th to 13th day, after which the epizootic in the foot-and-mouth-disease-afflicted herd comes to an end.

Natural immunity to foot-and-mouth disease, in Hondurey's opinion, is encountered very rarely among susceptible types of animals, and should be regarded as an exception. The individual instances of natural resistance to spontaneous infection with foot-and-mouth disease which are observed during an epizootic are evidently of different origin. It is impossible, finally, to deny the existence of "symptomless infection" in foot-and-mouth disease (suppressed forms). Noussu was one of the first to indicate that in foot-and-mouth disease it is necessary to reckon also with possible cases of symptomless forms of the disease.

Under experimental and practical conditions we have repeatedly had occasion to observe symptomless forms of infection. From one locality which had for many years been free of foot-and-mouth disease

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there were brought, as producers for obtaining anti-foot-and-mouth-disease serum, simmental cattle, a considerable portion of which developed the disease without visible clinical phenomena following artificial infection, and upon subsequent reinfection with the same strain of virus this same group of cattle remained clinically healthy.

The question of inherited immunity to foot-and-mouth disease is given inadequate illumination in modern literature on the subject. Hecker asserted that immunity of a mother which has had foot-and-mouth disease is always transmitted to the descendants. Frohner observed a case of immunity in a bull less than 4 years old, which had been transmitted to him by a mother which had had foot-and-mouth disease in the period of pregnancy. Orlov observed a case of the birth of pigs immune to foot-and-mouth disease on a farm where there had been foot-and-mouth disease 1.5 months before. He assumes that the mothers acquired active immunity in the period of pregnancy, in consequence of which pigs immune to foot-and-mouth disease were born.

Welasko asserts that inherited immunity is sufficiently stable and prolonged, the degree of intensity of inherited immunity usually depending on the period of pregnancy during which the pregnant mother had foot-and-mouth disease. If a cow, for example, had the disease long before calving, then the descendants' immunity to foot-and-mouth disease will be less prolonged. (Inherited immunity is not transmitted to the second generation from the mother, regardless of its degree of intensity and length of duration (Welasko).) According to data of the Riems Institute, inherited immunity in cattle is always passive, and lasts no longer than 14 days in the new-born young.

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It may be assumed that the stability and length of duration of inherited immunity depends also on the degree of development of the disease by the mother herself.

The influence of age on the formation of immunity to foot-and-mouth disease has been studied inadequately. So far it has been considered that young animals are more sensitive to foot-and-mouth disease than old ones. This has been explained by the fact that young animals are free of "vestiges" of previously acquired immunity, and also should be more sensitive to infection, particularly to foot-and-mouth-disease infection, due to physiological peculiarities caused by the growth and the development of the young system.

Waldmann and Rapp, studying the susceptibility to foot-and-mouth disease of guinea pigs, established that there exists in them an "inverse relationship" in the sense of sensitivity to foot-and-mouth disease: young guinea pigs no greater than 200-250 grams in weight prove to be little sensitive to foot-and-mouth disease, and older ones weighing 300 grams and more, on the other hand, are very sensitive to this infection. Young animals of milk-feeding ages (milk calves, and also calves no older than 4 to 6 months and sucking pigs aged up to 2 months) should be considered unconditionally as more sensitive to foot-and-mouth disease. At precisely this age the greatest mortality from foot-and-mouth disease is observed among young animals. Young animals of more advanced age are more resistant than adult animals.

The relatively high immunobiological resistance to foot-and-mouth disease of adult animals, particularly of cattle, which has often been pointed out by many investigators and practical workers,

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must be associated not so much with the age of animals as, evidently, with "vestiges" of previous immunity. According to Ogerov's data, when cattle developed the disease a second time (in 23 months) the course of foot-and-mouth disease in the same herd progressed much more weakly, with an inconsiderable number of cases of complications in the form of affliction of the extremities (17 percent). Sickness of the same animals for a third time (in 14 months) ran its course in still milder form. Some cows developed the disease barely perceptibly, and complications due to it were almost entirely lacking. Animals newly acquired by the farm, and which has not had foot-and-mouth disease before, suffered the disease very severely and with a considerable percentage of complications (lameness, etc.).

The breed of animals can evidently have a certain influence on the development of immunity, inasmuch as the degree of sensitivity to foot-and-mouth disease in various breed is not uniformly pronounced. It is known that highly bred types are more sensitive to foot-and-mouth disease than local indigenous cattle.

It is also possible that still other factors (shedding, nourishment, intercurrent infections, etc.) may exercise a certain influence on the formation and character of immunity, but all this remains so far inadequately studied with respect to foot-and-mouth disease.

The question of the type-specificity of immunity was elaborated earlier. It is essential to recall only that development of the disease by an animal, caused by a definite type of virus, causes immunity only to the homologous type. However, this statement is true only with respect to the guinea pig, which upon subsequent infection with all three types of virus develops the disease each time in a

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full 100 percent of cases. In cattle, upon cross-infection with virus of another type, it is possible to cause development of foot-and-mouth disease in no more than 85 percent of experimental animals (Trautwein and others). This is explained by the fact that in animals spontaneously susceptible to foot-and-mouth disease there are also formed together with homologous antibodies, heterogenous antibodies, while in guinea pigs evidently only homologous antibodies alone are formed.

In Great Britain, on the border with Ireland, there was in 1931 an outbreak of foot-and-mouth disease caused by type O virus. Animals which were immune to type O virus proved at the time of this epizootic to be resistant also to type C virus, which has caused the epizootic (English Commission). Depending on whether the animal is subsequently infected with virus of one type or another, it is possible to speak of monovalent (to one type of virus), bivalent (to two types of virus), and plurivalent (to three and more types of virus) immunity.

With virus infections, passive immunity is achieved by injecting immune-serum (hyperimmune or convalescent) into the system of the animal; however, its effect is of short duration (8--14 days, no longer). Anti-virus serums possess rather effective prophylactic properties, but their therapeutic importance is very small. They have a therapeutic effect only in the incubation period of the disease and during the first rises in temperature.

The mechanism of passive immunity in virus diseases has been studied very little. In passive immunization the anti-virus serums

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in the animal's system act directly on the cells of the latter, after which they are no longer infected.

Anti-virus serum, as demonstrated by Sabin's experiments on tissue cultures, is firmly absorbed on the cells, and only through prolonged washing is it possible to free them of serum, following which they become newly susceptible to the virus.

Sabin, injecting first the serum alone, and then virus, into the animal's system, established that under these conditions the virus cannot penetrate into the cells. When he injected the virus first, and then the serum, he succeeded in discovering virus inside the cells. With simultaneous injection of serum and virus the presence of the latter in the cells could not be discovered.

At present it has been proved possible to separate a completely neutral mixture of virus and the corresponding immune-serum. Sabin extracted the virus from a neutral mixture by centrifugation on a superpower centrifuge. Andrewes obtained the same results with the aid of absorption. Long and Olitsky extracted the virus from a neutral mixture by the method of cataphoresis. Gurevich and Yanushevich, in Academician Zil'ber's laboratory, extracted it with the aid of simple dilution of the neutral mixture 20 times, i.e. until destruction of the specific effect of the anti-serum and the appearance of the virulent properties of the virus.

All of these statements may be extended to a certain degree to the mechanism of formation of foot-and-mouth-disease immunity.

Subcutaneous or intramuscular injection of a sufficient dose of hyperimmune or convalescent serum inhibits generalization of the in-

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fection, but does not prevent the appearance of primary aphthae on the site of injection of the virus. Injection into the animal's system of large doses of serum also does not create complete immunity, and consequently, cannot prevent the appearance of primary aphthae on the site of introduction of the virus (Stockmann and Minett). Manninger asserts that passive immunization is able to provide protection only from generalization of the infection. Primary aphthae appear on the site of introduction of the virus even upon the injection of large amounts of immune-serum.

The injection of hyperimmune or convalescent serum and virus simultaneously, or in other words, simultaneous inoculations, causes a state of active immunity. The intensity and strength of immunity due to simultaneous inoculations depends on the nature of the reaction itself on the part of the animal's system. According to Pinto's data, complete immunity develops in animals after simultaneous inoculations only in the case where the animal develops foot-and-mouth disease, however, mildly, but with the phenomena of generalization of the infection.

If, then, generalization of the infection does not occur in inoculated animals, and only primary aphthae appear on the site of introduction of the virus, then immunity is always relative (partial). It can, consequently, protect the animal's system from generalization of the infection, but cannot prevent the appearance of primary aphthae on the site of introduction of the virus.

Immunity occurring after simultaneous inoculations which have been accompanied simultaneously by generalization of the infection,

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essentially differs in no respect from immunity caused by natural development of foot-and-mouth disease by the animal. The intensity of the reaction with simultaneous inoculations evidently absolutely does not depend on whether virus is injected into the animal simultaneously with the injection of serum, or following some elapsed interval of time (but within the limit of 12 days).

Stockmann and Minett injected experimental animals (cattle) with appropriate dosages, first of serum and on the following day of virus, given intramuscularly. Upon testing of the immunity in 48 and 116 days' time (by means of intramuscular injection of the same virus), all the animals remained healthy, i.e. all of them had acquired as a result of simultaneous inoculations a sufficiently stable and prolonged immunity.

In testing of the immunity of immunized animals or animals which have had the disease naturally, the site of injection of the virus has great significance (Vallee, Stockmann and Minett, Waldmann, Skomorokhov, and others).

The most reliable method of infection of cattle is the application of the virus on the scarified surface of the mucous membrane of the upper lip or of the oral cavity in general.

All other methods of infection are less effective. Intramuscular injection is not always effective, and therefore for most reliable infection in such cases it is always mandatory to injection large quantities of virus (Vallee and others).

In experiments with guinea pigs, intradermal injection of virus in the plantar surface of the rear extremities is the most convenient

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and effective method of infection (Waldmann and Trautwein, Stockmann and Minett, and others).

ANTI-FOOT-AND-MOUTH-DISEASE SERUM

Scientific elaboration of the problems of specific prophylaxis and therapy of foot-and-mouth disease, particularly in the first stages, has developed mainly in the direction of obtaining and applying an anti-foot-and-mouth-disease serum.

The application of vaccine in the countries of western Europe for the past decade, as shown by experience in combatting foot-and-mouth disease serum. However, in modern literature on the subject there are certain disagreements with respect to evaluation of anti-foot-and-mouth disease serum as a specific technique in the combatting of foot-and-mouth disease. However, the experience accumulated by many investigators in the application of anti-foot-and-mouth-disease serum shows that the serum may be applied successfully for prophylactic as well as therapeutic purposes, particularly in malignant foot-and-mouth disease, when mortality sometimes reaches considerable proportions.

In the countries of western Europe, passive immunization is applied mainly for prophylactic purposes on farms threatened with this disease, and also in the moving and transportation of cattle via rail and steamship. The Riems anti-foot-and-mouth-disease hyperimmune serum was at one time rather widely used in Germany and other countries of western Europe for purposes of creating a so-called prophylactic ring around the centers of foot-and-mouth disease.

In our country, anti-foot-and-mouth-disease serum and, in

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particular, convalescent serum have not found wide usage so far. (This is explained by many causes, but the principal of these stems from the difficulties of obtaining convalescent serum under the conditions imposed by the contaminated farm itself. These difficulties may be easily removed by means of the organization of special mobile laboratories, equipped with everything necessary for obtaining serum on the spot.) In the meantime it could be used with success on contaminated farms.

Anti-foot-and-mouth-disease serum may be used for prophylactic purposes through the passive immunization of those groups of animals on the contaminated farm which are housed separately from the common herd (milk-calves, young animals being given special treatment, pedigreed bulls, swine, and others, but which are exposed to the threat of infection. Unfortunately, passive immunization forms a short-term immunity in inoculated animals, no greater than 8 to 12 days. When the infection is present on the farm, such inoculations must be repeated several times.

Passive immunization does not create complete "absolute" immunity for the animal, as happens with vaccination, but creates only relative (humoral) immunity. Consequently, inoculation of the serum alone cannot protect the inoculated animals from the appearance of local irritations on the site of introduction of the virus. It is able to protect the animal only from generalization of the infection, which, however, is also very important, particularly with foot-and-mouth-disease infection of calves and young pigs. All this somewhat reduces the practical value of passive immunization as one of the methods of combatting foot-and-mouth disease.

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In a herd afflicted with foot-and-mouth disease, or individual groups of animals contaminated with the disease, the serum can be used in the form of combination (simultaneous) inoculations, i.e. simultaneously with the injection of the serum there is also performed an infection of the animal with the virus. Such inoculations are usually used as a forced measure for weakening a severe course of the disease and preventing mass losses due to foot-and-mouth disease, and also for curtailing the period of quarantine due to simultaneous, individual development of the disease by all adult cattle.

The immunity gained through combination inoculations in no way differs in principle from the immunity caused by natural development of the disease. The more strongly the animal's system reacts to them, the more stable the immunity caused by combination inoculations. With combination inoculations, complete immunity, as is well-known, develops only when the animals develop the disease with subsequent generalization of the infection as the result of inoculations (Pinto). Many authors consider that with a non-malignant course of foot-and-mouth disease there is no special necessity to resort to combination inoculations. According to Burgi's statement, combination inoculations do not exercise an influence on the course of the foot-and-mouth-disease process, if the disease runs its course in non-malignant form, but the inoculation always reduces the percentile mortality in the young.

The therapeutic importance of anti-foot-and-mouth-disease serum is small, since it is manifested only under the condition that it be used at the very beginning of the disease. Following the setting in of generalization of the infection in the system, injection of the serum

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for therapeutic purposes is no longer useful.

In practice, for combatting foot-and-mouth disease, hyperimmune serum and the serum or blood of animals which have had the disease are used.

After the discovery of plural types of foot-and-mouth-disease viruses the Riems Institute in Germany began to send out hyperimmune plurivalent serum, i.e. serum capable of exercising its effect against all three known types--O, A, and C.

Lobailly asserts that convalescent serum possesses the same activity as hyperimmune serum. Many other authors (De Winck, Van den Eichaut, Lichenberger and Ludwig, Baumgartner, Stohn), on the basis of their practical observations, do not see an essential difference in specific activity between convalescent serum and hyperimmune serum. In the experiments of the American Commission on Foot-and-mouth Disease, convalescent serum proved just as active as Loeffler hyperimmune serum obtained from the Riems Institute. Burgi asserts that the specific effect of both serums is almost uniform, and he was able to prove no essential difference between them in practice.

Waldmann and Trautwein, and also Gins and Krause, on the other hand, assert that the titer of convalescent serum is normally 6 to 20 times lower than the titer of hyperimmune serum. According to Waldmann's declaration, the Riems hyperimmune plurivalent serum is sent out with a titer of 0.48 cubic centimeters, and convalescent serum usually has a titer of 1.6 cubic centimeters.

Skomorokhov, Popova, Baydalin, and Peshekhonova once prepared a hyperimmune monovalent serum (type O) with titer 0.2--0.4 cubic

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centimeters. A hyperimmune plurivalent serum was prepared by Skomorokhov, Pepelkhonova, and Aristov with a titer of 0.4 cubic centimeters.

Lignieres in Argentina, in testing the immune properties of the Klems serum on guinea pigs, was able to establish its titer only in the range of 0.4 cubic centimeters. (Skomorokhov, on the basis of his previous investigations, performed in the Laboratory of Academician S. N. Vyshelesskiy (VIEV), considers that the titer of Klems anti-foot-and-mouth-disease hyperimmune serum was actually considerably lower than the "official" titer cited by Waldmann and his co-workers.) In recent years, Waldmann has not concealed the fact that hyperimmune plurivalent serum, particularly in combination inoculations, does not always produce uniformly satisfactory results, since "the required doses of serum and virus are as yet unknown". An insufficient dose of serum, according to Waldmann's report, cannot protect the animal from the disease, and a too large dose does not inhibit the development of the necessary reaction on the part of the system, and then formation of immunity does not occur.

Burgi considers that the results obtainable from use of hyperimmune anti-foot-and-mouth-disease serum often do not justify the losses connected with its usage. With prophylactic inoculations on farms of the threatened territory there occurred together with the successful results of the inoculations, in Burgi's words, failures. The seeming results usually attributed to the specific action of the serum were not always confirmed by tests.

Burgi considers that combatting foot-and-mouth disease with

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the aid of serum only protracts the course of the epizootic. Therefore, in Switzerland it has been necessary to give up mass inoculations with serum.

There are also extremely fundamental differences with respect to evaluation of the practical significance of the two serums-hyperimmune plurivalent and convalescent. Convalescent serum is used in a great many countries (Denmark, Holland, Belgium, France, Switzerland, Italy, and others), while hyperimmune plurivalent serum has found application mainly in Germany.

Cattle are used as producers for obtaining immune serums. Depending on the weight and other individual peculiarities of the animal, it is possible to get up to 6 to 8 liters of blood for one dose, which makes it possible to obtain up to 3 or 4 liters of prepared serum.

Very interesting is the report recently given by Hanon, who in his experiments with obtaining anti-foot-and-mouth-disease serum in vitro and in vivo demonstrated that horse serum is just as effective as hyperimmune serum from cattle.

CONVALESCENT SERUM

Convalescent serum has begun to be used very recently in the combat against foot-and-mouth disease. As early as 1896 Kitt used it as a practical method of combatting foot-and-mouth disease. Loeffler and Frosch, and also Loeffler and Uhlenhuth proved experimentally that the blood of animals which have had the disease contains specific antibodies. Study of the defensive properties of this serum has engaged very many investigators and practical workers (Hecker, Schutz,

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Ernst, Hillebrandt, Stoss, Kirner, Del Bono, Meiner, and others). Nogard, Roux, and also Vallee and Carre, on the basis of their investigations, came to the conclusion that the serum of convalescents possesses pronounced defensive properties.

In Denmark, during the epizootic of 1924-1925, 35 thousand head of cattle were inoculated for the purpose of attenuating the severe course of the disease and reducing mortality in calves and young pigs. In Switzerland, according to Burgi's report, more than 100 thousand head of cattle were inoculated with convalescent serum for 6 years.

Utilburg in Holland considers that the serum and blood of convalescents are a completely reliable method of combatting foot-and-mouth disease.

In Germany the Schleissheimer method of combatting foot-and-mouth disease, developed by Ernst and Drescher, enjoyed rather wide application at one time. It was applied in the form of simultaneous inoculations of the blood of animals which had recovered from foot-and-mouth disease, with simultaneous artificial infection. These inoculations, according to the report of Ernst and Drescher, cause a mild development of foot-and-mouth disease in the inoculated animals, without any unpleasant consequences or complications.

In Bavaria, for the purpose of reducing losses from malignant foot-and-mouth disease, the Schleissheimer method ("Bavarian forced inoculation") was used to inoculate 350 thousand head of cattle. As a result of the inoculations, mortality was only 0.27 percent among animals inoculated before generalization of the infection;

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among animals inoculated at the very beginning stage of disease at the time of the first temperature increases (i.e. with generalization already setting in) it was 0.75 percent; and among animals inoculated in the period of the appearance of secondary aphthae it was 4.04 percent. Among animals which had not been inoculated mortality was 1.6 percent with respect to the overall number of stock and 7 percent with respect to the afflicted herd (650,000 head were left uninoculated). Convalescent serum was used mainly for adult cattle. However, its protective properties were also proved in calves (Del Bono), swine (Zwick), sheep (Hirner), and goats (Zink and Sauer).

In the USSR, convalescent serum has been studied experimentally by Skomorokhov (1928), Bezzubets (1929), Ratner (1933), and others.

On the basis of our experiments, performed on cattle under experimental conditions, we have come to the conclusion that "convalescent serum possesses weaker defensive properties, but, when taken in increased doses, can substitute in defensive strength for hyperimmune anti-foot-and-mouth-disease serum". (Skomorokhov, A. L. "Obtaining Anti-foot-and-mouth-disease serum, and Its Practical Significance." Trudy Gos. inst. eksperim. veterin., t. 5, 1928.) Bezzubets treated 300 head of cattle with this serum under conditions of the practical campaign against foot-and-mouth disease, and obtained completely satisfactory results.

Ratner has used convalescent serum on cattle under the conditions of the practical campaign against foot-and-mouth disease and has come to the conclusion that "convalescent serum (serum from animals which have had foot-and-mouth disease) possesses sufficiently well-defined immune properties and can be used as a subsidiary method of combatting

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foot-and-mouth disease in the overall complex of other veterinary techniques". To obtain convalescent serum Ratner recommended using cattle specially infected for this purpose with a local strain of virus from the given epizootic. (As far as monovalent hyperimmune serum is concerned (type O), the author did not recommend using it without first establishing the type of virus causing a given epizootic.)

He, and also Dobrotvorskaya and Khomenko, in 1936-1937 again engaged in study of the practical value of convalescent serum, mainly in experience with combatting foot-and-mouth disease on farms where great mortality of calves and young pigs had been observed. The serum was tested on several hundred head of young animals, quite satisfactory results being obtained.

In later years, reports have appeared repeatedly which confirm the high practical value of convalescent serum in combatting foot-and-mouth disease. Savel'yev used convalescent serum with great success over the course of a number of years on large suburban animal-raising farms as an extremely reliable method of combatting losses among young cattle. He even applied it for the new-born, beginning with the first day of life and injecting 20-30 cubic centimeters daily for three days. By this means he succeeded in saving up to 85 percent of calves on the farm during a foot-and-mouth-disease outbreak. Positive results in using convalescent serum are also reported by Semayev. In an experiment on calves he obtained good results.

Interesting data on the use of convalescent serum have been obtained by Kindyakov. ("Results of the Scientific and Research Work of the Foot-and-mouth-disease Laboratory of the Kazakh Scientific-Research Veterinary Institute for the Years 1937--1942" (Manuscript).

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Beginning with 1941, large-scale observations on the use of convalescent serum were performed in Kazakhstan under the guidance of the Scientific-Research Veterinary Institute. The serum was used in four oblasts, mainly with young cattle (1143 liters of serum were prepared, which is sufficient for treatment of 30,000 head of young cattle). The serum was tested on farms contaminated with foot-and-mouth disease, on calves of less than 2 months in age and on young pigs.

In an experiment with the inoculation of pigs it was established that pigs inoculated upon the outbreak of foot-and-mouth disease on a farm all remained alive, and that pigs which were not inoculated perished. As a result of data collected by the Foot-and-mouth-disease Laboratory on the application of convalescent serum, Minayakov draws the conclusion that "anti-foot-and-mouth-disease serum of convalescents has justified itself in practice and is a specific method for the protection of young animals from foot-and-mouth disease". (It must be noted that the Foot-and-mouth-disease Laboratory of the Kazakh Scientific-Research Veterinary Institute developed and distributed a special "Precept on the Preparation and Application of Convalescent Serum", which made it possible to prepare the serum directly on the spot.)

With respect to the dose of convalescent serum which must be used for animals on farms contaminated with foot-and-mouth disease there are conflicting data. Finto considers that the degree of stability of immunity is in inverse proportion to the amount of serum injected into the animal's system, i.e. the more serum injected, the less pronounced the foot-and-mouth-disease process, and consequently, the weaker will be the immunity. And, conversely, the less serum used for inoculation, the more strongly pronounced will the reaction be,

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and consequently, the more intense and continuing will the immunity be. Burgi considers that in young cattle relatively small doses of serum give good results. In Switzerland, convalescent serum is used subcutaneously in the amount of 80 cubic centimeters for every 100 kilograms of live weight, the minimum dose being preferably no less than 300 cubic centimeters. In practice, in Burgi's opinion, much larger doses are used. With inoculations based on the Schleisheimer method, it is recommended that 100-200-300-400 cubic centimeters be used (0.5--1.0 cubic centimeters per kilogram of live weight). The serum is applied subcutaneously. If a noticeable improvement does not set in rapidly, the inoculation is repeated. Animals with high temperature are injected with larger doses than animals with normal temperature. It is recommended that sheep and goats be injected subcutaneously with 50--100 cubic centimeters. Inoculation based on the Schleisheimer method should be performed on the whole herd.

For adult cattle we have used convalescent serum in the amount of 400-500 cubic centimeters per head, and for young cattle, depending on age, from 20 to 100 cubic centimeters.

Rather used a doubled dose as compared with hyperimmune serum, i.e. used 20 cubic centimeters for 16 kilograms of live weight, but no less than 400 cubic centimeters per head of adult cattle. Semayev injected the young of cattle with convalescent serum in the proportion of 2 cubic centimeters for 1 kilogram of live weight.

More accurate with respect to dosage of serum is the proportion per kilogram of living weight of 1--1.5 cubic centimeters for calves and 1.5--2.0 cubic centimeters for young pigs and lambs.

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Convalescent serum is usually injected into the animal's system under the skin, having been heated to body temperature. It may also be used intravenously. Grand injected 200-400 cubic centimeters intravenously and obtained good results. This method can have still greater significance when it is applied for therapeutic purposes when it is necessary to achieve a rapidly effective action. It is very convenient, according to the statement of Arnst and Brescher, to inject the serum into cattle by the intraperitoneal method, (when the serum is injected intraperitoneally, the region of the "hunger" cavity on the left side serves as the site of injection.) which makes it possible to inject large quantities of it. In our own experience we have had repeated occasion to use this method as actually a very simple and convenient one.

It is recommended that blood for preparation of serum be used only after complete recovery of the animals, i.e. the disappearance of all symptoms of disease.

According to data of the American Commission, the appearance of antibodies in the blood of cattle which have had foot-and-mouth disease can be demonstrated beginning with the 6th day after the appearance of the first symptoms of disease. Terni considers that antibodies begin to disappear from the blood of animals which have been sick soon after the fever period.

Vallee and Carre recognize the most favorable moment for taking blood from animals which have had the disease as the 12th to 15th day after the appearance of the first symptons of the disease.

During the mass inoculations in Bavaria blood was usually taken

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for obtaining serum in the period of the 7th to 21st day after recovery.

Burgi considers that the best moment for taking blood for the preparation of serum is the 8th to 20th day after the appearance of the first clinical symptoms of foot-and-mouth disease.

Grand used blood from animals which had had the disease on the 12th to 13th day following the appearance of clinical symptoms of disease. He, and also Dobretvorskaya and Khomenko, used blood taken on the 8th to 14th day after recovery from animals which had had the disease for preparation of serum. Semayev considers it possible to take it on the 5th to 10th day after development of the disease.

On the basis of accumulated experience with the use of convalescent serum in our Soviet practice, it is recommended that blood be taken from animals which have had the disease no earlier than 12 or later than 20 days from the moment of discovery in them of clinical symptoms of foot-and-mouth disease, with the absence of any complications due to the disease.

The technique of obtaining blood and processing it into serum differs in no way in principle from the methods which are used with respect to the preparation of all other serums. (In preparing convalescent serum it is essential to use the "Precept on the Preparation and Application of Serum and Blood in Foot-and-mouth Disease", affirmed by the Glavvetuprum NKZ SSSR on July 26, 1943).

Certain partisans of broad practical application of convalescent serum in combatting foot-and-mouth disease consider that the technique

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of obtaining and preparing the serum is very simple, and see in this special advantages of this serum over the hyperimmune type.

Natner suggests that "the technique and method of obtaining the serum are extremely simple; however, to forestall the transmission of other infections they must be secured by the appropriate supervision, like every other preparation used in veterinary practice".

Actually, the technique of obtaining blood and serum is not quite so simple as it appears to certain investigators. With respect to obtaining the serum, the same requirements must be met as for all other bio-preparations developed in Soviet bio-factories.

For production of the serum in foreign countries (Denmark, Sweden, Germany, and others) special stations are organized with moving laboratories rigged with all types of modern laboratory technical equipment for obtaining blood from animals under farm conditions. In other countries (Holland, Argentina, and others) this business is centered in institutes only, which engage in the production of bio-preparations and under whose supervision the convalescent serum is used. Under the conditions in which we exist, the production and application of convalescent serum could be engaged in by outlying veterinary scientific-research institutes, experimental veterinary stations, and inter-rayonal veterinary-bacteriological laboratories.

It must be noted that the main worth of convalescent serum lies in the fact that it can be obtained and applied in the period of a single epizootic, and consequently, it will always be effective, independently of the existence of a plurality of types of virus. No less important is the fact that production of it is connected with the construction and organization of new bio-factories.

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The defibrinated blood of convalescents may be used instead of convalescent serum with the same success. According to Housseu's report, likewise that of Lamnare, the blood of convalescing animals was used on a large scale in France during the foot-and-mouth epizootic of 1934-1930, for the purpose of passive immunization. It may be injected into the animal's system by the same means as the serum. According to Houssu's data, it was injected intravenously in quantity of 10 to 100 cubic centimeters. Lamnare did 1906 transfusions of blood from convalescing animals. The blood may also be injected in defibrinated form.

For purposes of passive immunization against foot-and-mouth disease, Orlov injected in sucking-pigs the defibrinated blood of convalescent cattle. The blood was injected under the skin in quantity of 2 to 4 cubic centimeters, and of 40 to 60 cubic centimeters for nursing sows. In all 56 sucking-pigs were inoculated, of which 34 head (60.8 percent) remained healthy, 11 (19.6 percent) became sick but recovered, and 11 (19.6 percent) died. At the same time uninoculated pigs, a group of 33, all died (100 percent). Orlov draws from this the conclusion that "defibrinated blood, taken shortly (on the 7th to 10th day) after recovery, possesses protective and curative action with respect to sucking-pigs". In essence, defibrinated blood possesses the same assets and shortcomings as convalescent serum.

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HYPERIMMUNE MONOVALENT SERUM

Loeffler and Frosch, likewise Loeffler and Uhlenhuth, proved the possibility of obtaining serum with hyperimmune properties by repeated injection into animals which had had the disease of increasing quantities of virus in the form of the content of foot-and-mouth disease vesicles ("lymph virus"). The accomplished hyperimmunization of animals by means of intravenous injection of increasing amounts of virus from aphthae from swine in three doses at intervals of 7 days. Loeffler and Uhlenhuth used from 50 to 60 cubic centimeters of virus for hyperimmunization of one animal. Many investigators in other countries (Nocard and Roux, Mousso, Vallee, Lesboa, de Reja, Lignieres, and others) have confirmed Loeffler's and Uhlenhuth's data.

The hyperimmune anti-foot-and-mouth disease serum obtained by the first investigators not infrequently did not exercise a specific effect in practice. These phenomena, which were then difficult to explain, became comprehensible only after the plurality of foot-and-mouth disease virus-types was discovered. Loeffler serum, being monovalent, naturally proved to be active only against the homologous type of virus. This was evidently the cause of the failures which placed in doubt the practical significance of Loeffler serum.

There were also attempts to obtain hyperimmune foot-and-mouth disease serum in prerevolutionary Russia (Ekkert commission, 1902), but all of these proved unsuccessful.

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In the USSR in 1927, the author, under the guidance of Academician Vyshelesskiy, first obtained hyperimmune monovalent serum, which proved to be specific and highly active. The hyper-immunization of animals was performed in 2 to 3 doses at intervals of 10 to 14 days, by means of intraperitoneal injection of virulent blood from sick animals. Each animal was injected once, with the aid of a Bobrov apparatus, with 3 to 4 liters of virulent blood obtained from animals specially infected for this purpose at the moment of highest temperature. In 10 to 11 days following the last injection of virulent blood, blood was taken from the animals for obtaining serum and testing its activity.

The titer of the serum was first established on guinea pigs, and subsequently its activity, moreover, was tested on cattle under the conditions of a foot-and-mouth disease epizootic. In simultaneous inoculations, the serum was injected subcutaneously in the proportion of 10 cubic centimeters for 16 kilograms of live weight. Simultaneously, artificial infection was formed by means of applying the virus to the scarified surface of the membrane of the upper lip.

The results of the test were fully satisfactory. This method of obtaining hyperimmune serum first seemed extremely tempting, as very simple and not requiring expensive virus breeders, However, we later had to give it up as little suited to factory production.

In our experiments we succeeded above all in proving the

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possibility of obtaining hyperimmune serum. Subsequently it was necessary to alter the method itself of hyperimmunization of animals (producers), which was later done.

Ruppert and Rottgardt, simultaneously and independently of us, obtained an anti-foot-and-mouth disease serum using fundamentally the same method. They used virus for hyperimmunization of animals taken from a heifer specially infected for this purpose. In 36 hours following infection, during a high increase in temperature, they took blood from the heifer and injected it into another animal (the producers): first 6 liters, and the second time 8 liters of virulent blood. In 14 days they took blood from the hyperimmunized animals for preparation of serum, and checked the latter as to activity. In testing at the Riems Institute it was established that the titer of the serum obtained by Ruppert and Rottgardt was 0.1 cubic centimeters, while normal serum, even in a quantity of 12 cubic centimeters, did not possess such defensive properties, and convalescent serum had a titer of 0.6 cubic centimeters.

In 1932, in the Foot-and-Mouth Disease Institute, the author and his co-workers (Popova, Baydalin, and Peshekhonova) obtained hyperimmune monovalent serum by means of treating cattle with increasing quantities of virus. For this purpose the virus was gathered from foot-and-mouth disease vesicles (aphthae) of swine specially infected for this purpose. Serum was obtained with a rather high titer (0.2 to 0.4 cubic centimeters). As a basis for the method of hyperimmunization of animals the author used the old

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Loeffler method, but modified considerably in the interests of less costly production.

Hyperimmunization was performed by means of thrice-repeated intravenous injections of virus ("lymph"): the first time 0.1 cubic centimeters, the second time 5 cubic centimeters, and the third time 10 cubic centimeters. Following the third injection, blood was taken from each animal in order to find out the titer of the serum in the group. On the day following the taking of blood all animals were injected with virus in the amount of 10 cubic centimeters (the "booster" dose). In all instances the virus was used in dilution of 1:10. In order to avoid phenomena of anaphylaxis with the third injection, and also with later "booster" doses, 50 cubic centimeters of virus, diluted 1:10, were injected under the skin, and in 24 hours a full dose of virus was injected intravenously. The virus was injected in several doses at intervals of 1 to 2 minutes.

Titration of the serum was performed on guinea pigs according to Waldmann's and Pape's method. For titration of the serum, guinea pigs of standard weight 300 to 420 grams were used. For each titration of the serum it was necessary to use no less than 15 to 21 guinea pigs. For testing for activity, the following amounts of serum were used: 0.1 to 0.2; 0.4; 0.6; 0.8 cubic centimeters. The guinea pigs, which were injected subcutaneously with these quantities of serum, were infected simultaneously by application of foot-and-mouth disease virus to the plantar surface of the

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skin of a rear extremity. The minimum amount of serum which prevented generalization of infection in the guinea pig was computed by its titer.

The serum obtained was injected for prophylactic purposes into adult cattle in the proportion of 20 cubic centimeters for 1 quinteal of live weight, but no less than 200 cubic centimeters per head, into young cattle from 6 months to 1 year of age in the amount of 50 to 150 cubic centimeters, into calves in the amount of 40 centimeters, into sheep and goats in the amount of 40 centimeters, into adult swine in the proportion of 30 cubic centimeters for 1 quintal of live weight, but no less than 40 cubic centimeters, and into young pigs with live weight up to 4 to 8 kilograms in the amount of no less than 10 to 15 cubic centimeters. With summltaneous inoculations in adult cattle and swine the serum was used in the amount of 8 to 10 cubic centimeters for each quintal of live weight, but no less than 50 cubic centimeters per head. Calves, sheep, and goats were injected with 30 cubic centimeters, as a minimum dose, and sucking-pigs with 5 to10 cubic centimeters.

Wide-scale testing of the serum under the practical conditions of combatting foot-and-mouth disease has shown that it possesses sufficiently well-pronounced defensive properties and could have practical significance under certain conditions. In application of it in practice there have been individual failures, but they are not connected with the quality of the serum itself.

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The cause of the failures was evidently connected with the presence of other variants (perhaps even types) in the same locality where the serum was used.

Hyperimmune plurivalent serum should provide better results in practice than hyperimmune monovalent serum, but even it, as is well-known, does not possess absolute prophylactic effect. J. Lignieres considered possible the preparation of hyperimmune polyvalent serum by means of simple mixing of monovalent serums obtained from hyperimmune animals treated with different types of virus.

PLURIVALENT SERUM

After the three types of virus -- O, A, and C -- were discovered, they began on Riems Island to produce (after 1926) hyperimmune plurivalent serum. It was obtained on the basis of successive treatment of animals (producers) with viruses of all three types -- O, A, and C -- in the course of 6 to 8 weeks at intervals of 14 days (Waldmann). The basis of hyperimmunization of animals with viruses of all three types is the old Loeffler method, altered in form by Waldmann.

For practical use, the serum is produced on Riems Island with a titer of 0.4 cubic centimeters. Practical importance has mainly been acquired by hyperimmune plurivalent serum in Germany, where it has been used widely for prophylactic purposes. In 1926 in Germany 21,359 head of pedigreed stock (cattle, sheep, swine,

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and goats) were inoculated with Riems serum for prophylactic purposes. In 1927, 21,359 head of exhibition stock and 142,129 head of stock at bazaars and cattle-markets were inoculated. (In spite of the wide scale of application of hyperimmune pluri-valent serum in Germany in these years, the spread of foot-and-mouth disease did not decrease with respect to preceding years.) In 1928, Zehl and Tiarks treated 11,814 head of stock at 24 markets for prophylactic purposes. Instances of communication of foot-and-mouth disease at these markets were noted 9 times, but outbreaks of the latter did not occur. The authors are inclined to attribute this to the prophylactic effect of the serum.

For passive immunization with Riems serum, the following doses are recommended: for adult cattle, 20 cubic centimeters per quintal of live weight, but no less than 200 cubic centimeters; for younger animals, 15 to 150 cubic centimeters (depending on age and weight); for calves, 40 cubic centimeters; for sheep and goats, 40 cubic centimeters; for young pigs weighing up to 12 kilograms, 10 to 15 cubic centimeters. With simultaneous inoculations, the following doses are recommended: for cattle, 8 to 10 cubic centimeters per quintal of live weight; for calves, sheep, and goats, 30 cubic centimeters apiece; and for young pigs, 5 to 20 cubic centimeters apiece. With malignant foot-and-mouth disease the dose of serum in simultaneous inoculations may be increased.

In the German press many articles were published annually, devoted to evaluation of the practical importance of widespread application of Riems hyperimmune serum for prophylactic purposes,

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wherein its "high immunizing qualities" were praised. However, in spite of such broad application of this serum, an average of 46,000 points contaminated with foot-and-mouth disease were noted annually in Germany.

The Riems Institute, on the basis of experimental study of the immunizing properties of Riems serum, reached the conclusion that "Riems hyperimmune plurivalent serum possesses extremely weak protective action. The serum does not immunize against the majority of strains of virus encountered in England". Experiments were performed on cattle, sheep, and guinea pigs. The serum was injected in larger does than were envisaged by the precepts of the Riems Institute, but it did not protect the inoculated animals from either artificial or natural infection in 24 hours. In testing the serum on guinea pigs it turned out that the latter did not acquire immunity with respect to standard types O and A.

Questions of the practical application of hyperimmune plurivalent serum were given much attention at the Eleventh International Veterinary Congress in London; however, use of the serum was almost confined in practice to the borders of Germany, which was indeed the monopolistic supplier of this serum.

In the USSR, a method of obtaining hyperimmune plurivalent serum was developed, as already indicated, in the Foot-and-Mouth Disease Institute by the author, Peshekhonova, and Aristov, on the basis of the method of the Riems Institute. Serum was obtained with a titer of 0.4 cubic centimeters. Testing of the serum in the practical campaign against foot-and-mouth disease confirmed its immunizing properties.

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Later a change was introduced in Germany in the method of obtaining Rieme hyperimmune plurivalent serum: instead of virus from pigs, they began to use cultured virus for hyper-immunization of animals. The method of hyperimmunization through the use of cultured virus has not been published.

At the Twelfth Session of the International Epizootic Bureau in Paris on the problem of measures against foot-and-mouth disease, it was stated in a resolution that "in the interests of prophylaxis of foot-and-mouth disease already-known methods are recommended, in the form of passive immunization and the application of simultaneous inoculations. On farms threatened with foot-and-mouth disease it is essential to perform passive immunization of animals susceptible to foot-and-mouth disease. The application of these methods may depend on individual cases on location conditions".

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ACTIVE IMMUNIZATION. VACCINATION

The problem of immunization in virus infections is one of the most interesting in modern biology. The difficulties of solving this problem stem above all from the fact that the very nature of the causal agents of these infections remains poorly illumined, and cultivation of them is possible only in tissue media (in the presence of living tissues).

In spite of this, virus vaccines have begun to be used for prophylactic purposes with virus infections, in medical as well as veterinary practice.

It must be considered that the problem of active immunization has been solved for foot-and-mouth disease, too, although practical adaptation of this new method is fraught with very great difficulties.

Large-scale investigations into the solution of the problem of active immunization against foot-and-mouth disease have been performed not only in foreign countries (France, Germany, Denmark, and others), but also in the USSR (Skomorokhov and associates, Ratner, Kindyakov and Doronin, Savel'yev, and others).

For the past 10 to 20 years rich material has been accumulated on the question of immunization, which permits us to draw the following conclusions:

1. Stable and prolonged immunity in foot-and-mouth disease is possible only as the result of active reaction of the organism on the injected foot-and-mouth-disease antigen; between the intensity of the system's reaction and the intensity and character of immunity

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there exists a direct relationship.

2. The formation of immunity is possible without the appearance of specific afflictions in the form of aphthae, and also without noticeable temperature reaction.

3. Previously killed virus loses its antigenic properties and is unsuitable or, in any case, poorly suited for active immunization.

The treatment of virus with various chemical substances for the purpose of obtaining vaccine should be performed within sharply defined limits, within which it is possible to inactivate the virus without destroying at the same time the antigenic structure of the virus itself. Evidently this is the basis of the difficulties of obtaining highly effective anti-foot-and-mouth disease vaccine, for there is so far no knowledge of the limits within which it is possible to attenuate the virulent properties, or in other words, beyond which destruction of the antigenic structure of the virus sets in.

Evidently, the problem of active immunization can be conclusively solved only through the application of virus which is living but which is attenuated almost to the point of complete inactivation.

Haudurey offers the following indications on this question: "With the help of virus which has been killed, apparently, it has not yet been possible to attain protection from ultravirus disease. Jenner used living vaccinal virus, Pasteur the living virus of hydrophobia. Everywhere, with no matter what infection, indisputable

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results have been obtained only from application of living virus, where only this has been possible. It is true that in some cases it has been possible to vaccinate with inframicrobes (ultra-viruses - A. S.) treated with formalin, carbolic acid, and others. However, had these viruses been killed? Klieger," Haudurey says further, "studying the vaccine of smallpox-diphtheria in fowl, which had been held to consist of viruses which had been killed, subjected the latter to cataphoresis and obtained virus in the living state at one of the poles. Consequently the virus, which had been considered to have been killed, proves to be not killed at all -- it was only in very small quantity, so infinitesimal that injection of it did not cause any infection, but at the same time created immunity... It may almost be said with certainty that with other ultravirus diseases, too, the same result would be obtained with the use of formolized, carbolized, even heated viruses, upon the condition that these vaccines should actually immunize the animals... Vaccination with such methods is exclusively a question of dosage of the given virus". (Paul Haudurey. "Pathogenetic and Sapropaylic Ultraviruses." Translation from the second French edition. Biomedgiz, 1935, page 342.)

And further, Haudurey draws the following conclusion: "In inframicrobic infections immunity cannot be obtained with any other method than that of living viruses. Two methods are recommended for the preparation of vaccines: one consists of dosage of a number of virulent elements by means of dilution, careful heating, and special chemical substances in appropriate doses; the second consists of the application of viruses which have been modified and attenuated

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in their pathogenic effect by means of passages through an animal organism of another type than that normally susceptible to the given disease".

Rivers considers that "only active, living virus protects against the same virus injected a second time... In other words, with few exceptions it is extremely doubtful that by means of completely inactivated virus it would be possible to protect against the same virus. The use of active virus, either in small quantities or in attenuated state, is the only method by which it is possible to achieve prolonged protection." (Rivers. "Some General Views of Filterable Viruses." From the book "Filterable Viruses". Sel'khozgiz, 1934, pages 11 - 29.)

The well-known Soviet immunologist Academician Gamaleya says that "with the aid of viruses which have been killed it is extremely difficult to cause immunity. Up to the present it has not been clear whether it is possible to obtain any degree of stable immunity by means of viruses which have been killed... There are cases where the virus is supposedly killed with formalin and does not cause disease in any form, but, nevertheless, if it is subjected to cataphoresis living virus may be found on the anode". (From Gamaleya's report, "Immunity in Virus Diseases". Trudy Vsesoyuzn. soveshch. po izuch. ul'tramikrobov i fil'truyushch. virusov. Izd. Akad. nauk SSSR, 1937, pages 131 - 137.)

Another outstanding Soviet investigator, Academician Zil'ber, considers that the possibility should not be ignored of reproduction of immunity with the aid of inactivated virus, at least in some

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infections, but the intensity of such immunity is always very small. "Inactivated viruses," says Zil'ber, "can achieve practical importance as vaccines which prepare the system for subsequent injection of vaccines from living, attenuated, or altered viruses".

So far, no one has succeeded in proving the possibility of formation of stable and prolonged immunity to foot-and-mouth disease in animals treated for the purpose of immunization with virus which had been killed.

Loeffler was one of the first to make an attempt to immunize cattle with virus ("lymph") heated to 60 degrees. Many investigators after him used killed, or as it was called then, "sterilized" virus for immunization, but all these attempts have proved unsuccessful.

"Essentially no one has accepted the idea," says Vallee, "of the possibility of vaccination against foot-and-mouth disease with only killed virus alone." The American Commission on Foot-and Mouth Disease, on the basis of its experiments, came to the conclusion that avirulent material does not impart immunity. (Olitsky. "Foot-and-Mouth Disease and Vesicular Stomatitis." In Kiver's book, "Filterable Viruses". Sel'khozgiz, 1934, pages 125 - 142.)

According to Andrewes' data, immunity can occur only as the result of the reaction of the organism on living virus which has not been subjected to profound change, and the animal very soon after such inoculation becomes immune, independently of the degree and character of the reaction itself. Trautwein also considers not very probable the possibility of biological occurrence of immunity

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upon injection of an antigen which has been killed.

At present it may be considered proved that the injection of subinfectious doses of virus into the systems of animals susceptible to foot-and-mouth disease involves the formation of immunity. Specifically, the English commission came to the conclusion that subinfectious doses of virus cause a state of immunity in experimental animals. Galea, in his experiments, had occasion to become convinced that injection of subinfectious doses of virus in experimental animals brings about the formation of immunity.

The statements of individual investigators given here seem completely convincing and make it possible to form the conclusion that sufficiently effective and reliable active immunization is possible, evidently, only through the use of living virus which has been attenuated toward complete inactivation.

Muromtsev adheres to another view with respect to active immunization in virus infections. He considers that "the process of redevelopment of the system to an immune state with respect to any infection cannot be separated from the destruction of the causal agent of this infection in the system. These processes can in no way be distinguished from each other. Hence, only this conclusion may be drawn: without destruction of the causal agent of disease in the system it is impossible for immunity to be created, and consequently, immunity is created only by a dead antigen". (Muromtsev, S. N., "A New Principle for the Preparation of Vaccines (Semi-fluid Vaccines)." Sel'khozgiz, 1938, pages 30 - 31.)

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In another place he expresses the following thoughts on the same question: "The impossibility of vaccination with antigens which have been killed has been shaken incomparably more seriously than the impossibility of cultivating them without live cells".

It would be possible to cite numerous examples, not only of experiments, but also of results of successful practical application of dead vaccines in all types of ultravirus diseases: pantropic, neurotropic, pneumotropic, and dermotropic. Inoculations of formalinized vaccine against swine fever in millions of animals in Japan, following the work of Teracado (1918), and inoculations with the same vaccines in Austria by Michalka were justified by practical results.

The anti-cattle-plague formolé-vaccines of Curasson and Tassin create immunity for 9 to 12 months, which has been proved not only by experimental projects, but also by experience with inoculations in practice. The formalinized anti-foot-and-mouth-disease vaccine of Waldmann (1936 - 1938), upon testing on hundreds of thousands of animals, proved capable of protecting them for 4 to 5 months. For rabies, it must be considered conclusively established that virus which has been killed gives quick and stable immunity, and since 1938 formalinized antirabies vaccine has already found broad application, particularly in Indo-China. The formalinized vaccine against encephalomyelitis in humans proposed by the VIEM (Smorodintsev and others) has thoroughly justified itself in practice." (Muromtsev, S. N. "Semifluid Vaccines." Sel'khozgiz, 1944, pages 86 - 92.)

"On the basis of the results of all these projects," says Muromtsev, "it is difficult to agree with the categorical assertion that in

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ultravirus infections immunity can be obtained only with the aid of the living virus."

Muromtsev came to these conclusions on the basis of his extremely interesting and practically valuable research with respect to preparation of semifluid, killed vaccines which he had obtained as the result of study of the action of the physiochemical properties of the medium on the activity of various bio-preparations. No less interesting are the results which he obtained in preliminary experiments on the study of the effectiveness of killed, semi-fluid virus vaccines. But, unfortunately, the results of these experiments do not provide bases for final conclusions. Research in this field is still in the stage of preliminary development.

Large-scale work in the field of active immunization against foot-and-mouth disease by means of the application of inactivated virus has been carried out in France (Vallee, Carre and Rinjard, Valle and Bridre, Richard, Galea, Khomutov, and others), in England (Bedson, Maitland, and Durbury), in Denmark (Schmidt and Hansen, Schmit-Jensen, and others), in Argentina (J. Lignieres, R. Lignieres), in Holland (Monteil, Frenkel, and Van Vaveren, Toussieng and Fogedby), in the USSR (Skomorokhov, and also Lavrovskiy and Dobrotvorskaya, Rafalovich, Lavrovskiy and Volkov, Savel'yev, Maslov, Yuskovets, Mirotvorskiy, Babich and Lipatov, Ratner, Kindyakov and Doronin, Dubyanskiy and Khomenko, and others).

Many investigators have long held that the essential condition of the occurrence of a stable and prolonged immunity is an active reaction on the part of the system, in the form of the formation of even only one quickly disappearing local aphtha on

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the site of introduction of the virus, and a necessary fever reaction in the form of a temperature rise (Vallee, De Blieck, and others).

According to Vallee, in some cases, particularly with the injection of large amounts of virus intravenously or subcutaneously, no visible reaction is observed in the animal, and in such an instance it does not acquire immunity. However, in individual instances Vallee observed the formation of immunity without the appearance of any reaction (aphtha) at all on the site of introduction of the virus, but the value of such immunity is in his opinion small.

Waldmann and Trautwein have likewise long considered that "the formation of active immunity is possible only in those animals in which upon injection of virus in the membrane of the buccal cavity a local reaction is observed on the site of injection". Much later, Waldmann and Reppin, in one of the reports "On the Question of Active Immunization" (1935), expressed a somewhat different point of view on this question: "Active immunization of cattle without visible clinical development of foot-and-mouth disease is fully possible. For the formation of immunity a reaction, however small, is necessary in the form of a mild fever condition. However, more stable immunity is formed only upon development of the disease with the appearance of primary aphthae on the site of infection, or with generalization of the infection".

Certain investigators long ago noted that it is easier to cause humoral immunity to foot-and-mouth disease than a state of complete immunity, i.e. with the presence of not only humoral, but also tissue factors. Valle considered that general humoral immunity

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can be caused without the presence of any visible reaction on the part of the animal's system, while tissue (local) immunity is impossible without the formation of a local reaction on the site of injection of the virus or of a general fever reaction on the part of the system. The American commission at one time drew the conclusion that "the application for immunization of insufficiently attenuated or strong (non-attenuated) virus inevitably involves a reaction on the part of the animal's system such that it is accompanied by the clinical symptoms of foot-and-mouth disease".

These views on the conditions of the formation of active immunity to foot-and-mouth disease, which have been supported by such outstanding investigators of foot-and-mouth disease as Vallee, Waldmann, De Blieck, the American commission, and others, for a long time misled investigators in the field of the development of methods of active immunization against foot-and-mouth disease, and created for some time a certain lack of perspective in the solution of this all-important problem.

However, some investigators (Andrewes, Lignieres, Jalea, Skomorokhov, and others) have considered that the occurrence of immunity to foot-and-mouth disease is fully possible without the appearance of clinically visible reaction on the part of the system, specifically, without the formation of aphthae.

On the basis of his investigations, Andrewes came to the conclusion that immunity to foot-and-mouth disease in animals may be achieved without the formation of aphthae, that it may be intensified and made more stable through the use of repeated inoculations of foot-and-mouth-disease antigen which at the same time does not cause the

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appearance in animals of aphthae or other visible reaction. Galea suggests that for the formation of active immunity against foot-and-mouth disease by means of the application of living, un-"modified" antigen the presence of specific changes in the form of the appearance of aphthae is not a necessary condition.

Toussieng and Fogedby, and also Frenkel and Van Vaveren, consider that the occurrence of immunity is possible without the appearance of any clinical symptoms of the disease. They came to such a conclusion on the basis of experiments in immunization of cattle and swine.

The numerous data of Soviet and foreign investigators now leave no doubt that active immunity to foot-and-mouth disease is possible without the appearance of aphthae (Skomorokhov, Lavrovskiy and Dobrotvorskaya, Kindyakov and Doronin, Rafalovich, Mirotvorskiy, Dubyanskiy and Khomenko, Ratner, Waldmann and Köbe, Galea, the English commission on foot-and-mouth disease, and others).

Waldmann, Köbe, and Pyl published at one time the results of their experiments on active immunization of cattle with formolé-vaccine, in which they approached differently the evaluation of the role of local reaction in the formation of immunity: "for the formation of immunity to foot-and-mouth disease reaction on the part of the system in the form of a fever state is not essential". This conclusion, made by Waldmann, who long held an opposite position on this question, was a considerable forward-step in the matter of the successful solution of the problem of active immunization.

There are many conflicting data on the question as to which

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of the existing methods of injection of foot-and-mouth-disease antigen into the animal's system for the purpose of active immunization is the least dangerous, and at the same time sufficiently effective.

Many investigators injected the virus intravenously for the purpose of immunization, as a result of which a general reaction set in. It was accompanied by a prolonged temperature reaction, sometimes without subsequent appearance of aphthous irritations (Lebailly, J. Lignieres, Cosco and Aguzzi, Mousau, De Blieck and Winkel, and others). According to Vallee's data, intravenous injection of the virus either causes disease or does not cause it, but in the latter case formation of immunity does not occur. The presence or absence of temperature reaction does not furnish justification for conclusion as to the practical value of this method of injection of the virus. The system's reaction to intravenous injection of the virus is not in itself sufficient for the formation of immunity.

Some investigators, in experiments on active immunization against foot-and-mouth disease, have used the subcutaneous method of injection of the antigen (Nossotty, Loeffler, Roux, Nocard, and others). Later, Valee, Carre and Rinjard, Richart, Celormini and Harispe, and also Skomorokhov, Lavrovskiy, and others also used in turn the subcutaneous method of active immunization and obtained more or less satisfactory results. With experimental infection of animals with virus the subcutaneous method, as is known, is considered poorly reliable. Even with active immunization against foot-and-mouth disease the subcutaneous method of injection of antigen evidently does not always give uniform and reliable results. Vallee later began to

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perform subcutaneous inoculations of antigen (formolé-vaccine) twice, and obtained more favorable results. (Personal communication of Professor Vallee (1929).)

In the search for more effective methods of injection of vaccine into the animal's system we have applied the intradermal method of active immunization against foot-and-mouth disease, which has given better results than the subcutaneous method (1929). "It is inherently obvious that vaccination against foot-and-mouth disease by the intradermal method presents a very interesting problem. Perhaps it will be possible by such a method to cause the formation of more stable immunity in a shorter time, if a sufficient quantity of vaccine is used" (Vallee). (Personal communication of Professor Vallee (1929).) "It seems to me that the intradermal method of injection of vaccine may be able to make it possible to achieve a result more easily than any other. But it is essential that anti-foot-and-mouth-disease vaccine be completely harmless" (Bezredko). (Personal communication of Professor Bezredko (1929).)

Vallée, as may be seen from his report, as early as 1926 was studying the method of intradermal immunization, but in a small experiment on only 4 head of cattle in all obtained negative results, and afterwards did not return to it. Van Saceghem, as early as 1924 during the epizootic of foot-and-mouth disease in West Africa, in research on a method of active immunization attempted interdermal injection of the virus and became convinced that it causes more severe sickness in animals by comparison with infection through the mucous membranes of the buccal cavity or with subcutaneous injection of virus. On the basis of his experiments, the author came then to the conclusion that vaccination against foot-and-mouth disease

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With intradermal injection of the virus due to slow resorption of the latter in the skin has great advantages and can be effected successfully with the aid of attenuated virus. Unfortunately, this report of Van Saseghem did not attract attention to itself at the time, and only, beginning in 1929, after publication of Skomorokhov's data did some investigators begin to be interested in the method of intradermal immunization.

In the comparative experiments of Waldmann, Köbe, and Pyl (1937), which they performed on guinea pigs with the subcutaneous method, it was possible to immunize only 35 percent in all, while with intracutaneous and intraperitoneal injection it was possible to immunize all a full 100 percent. With subcutaneous immunization of guinea pigs with chloroform antigen Galea obtained less favorable results than with intracutaneous injection of it. The English commission, studying methods of active immunization under experimental conditions, used intramuscular injection of the vaccine, and on guinea pigs obtained completely satisfactory results.

Waldmann, Köbe, and Pyl were able, with intramuscular injection of vaccine, to immunize 85 percent of guinea pigs. Incidentally, the authors consider it proved that with intramuscular infection more virus is always needed than with usual methods of infection. The authors came to this conclusion after study of intramuscular injection of the virus in cattle.

J. and R. Lignieres developed an original method of active immunization by means of intracutaneous injection of attenuated

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virus in a zone immunized in preliminary with hyperimmune serum. Calca applied this same method of Lignieres, with small changes, on guinea pigs, only that instead of immune serum for the creation of an immunizing zone he used chloroform-antigen and obtained extremely satisfactory results.

Together with these methods of injecting antigen into the animal's system, other combinations are obviously possible; intracutaneous with subcutaneous, or intramuscular with intracutaneous, intraperitoneal with one of the injections indicated, etc.

The problem of methods of preparing vaccine, in spite of definite achievements in this domain, continues to attract the attention of modern investigators. Attenuation of the virus and inactivation of it right up to complete loss of virulence can be achieved with the help of physical and chemical methods, or finally, by means of sensitizing the virus with a specific serum. Some investigators have worked a rather long time on obtaining symbiotic vaccine with the aid of biological methods of attenuation of the virus (Duclaux, Rinjard and Cordier, and also Belen and others).

Attempts to inactivate the virus by means of high temperature have been undertaken by many investigators, but they must be acknowledged in general to have been unsuccessful.

According to Maitland's data, formol-vaccine at a temperature of 55 degrees Centigrade loses its immunizing properties in as little as 45 minutes. However, the same author succeeded in inactivating virus in a thermostat at 37 degrees Centigrade in the course of 5 days (at pH 7.6), the virus losing its antigenic properties to only an

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insignificant degree. Upon drying, the virus, as a rule, loses its antigenic properties.

Waldmann and Reppin prepared vaccine from virus desiccated by means of a vacuum machine, the virus being taken in the form of the "lymph" of aphthae. It was possible to inactivate the virus in this fashion, but at the same time its antigenic properties were lost to a considerable degree. Tests of the immunizing properties of the vaccine performed on guinea pigs showed that it did possess such properties. Waldmann, Köbe, and Pyl, for obtaining a stable and concentrated preparation, desiccated the virus by means of cold. The vaccine thus obtained had almost thoroughly preserved its antigenic properties, but in one instance out of nine it lost them completely.

Many investigators, in order to inactivate the virus, have used various chemical substances. Vallee, Carre, and Rinjard, so it seems, first suggested formalin for this purpose, which according to the data of these authors kills the virus without destroying its antigenic structure. They developed a method and technique of obtaining formolé-vaccine which was later verified by other investigators.

In the USSR formolé-vaccine, prepared according to the method of Vallee, Carre, and Rinjard, was first used by the author in experiments on cattle.

In England first Bedson, Maitland, and Burbury, and later Maitland, developed independently a method of preparation of formolé-vaccine. In experiments on guinea pigs this formolé-vaccine gave

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completely satisfactory results.

Galea, and also Khomutov, in order to activate the virus used chloroform, which, as shown by the experiments, does not destroy the antigenic structure of the virus. With guinea pigs they proved the possibility of immunization against foot-and-mouth disease with chloroform-vaccine.

In Denmark, Schmidt, Hansen, and Schmit-Jensen (1934) developed an original method of inactivation of the virus by means of adsorption of the latter with aluminum hydroxide and addition to the adsorbate obtained of formalin. With guinea pigs they proved that such a vaccine possesses high antigenic properties.

In Germany, Waldmann and Köbe (1937) introduced certain changes into the method of preparing the vaccine which has been developed by the Danish investigators. As a new component for the preparation of vaccine they introduced a glycol buffer (with value pH 9.0), and for inactivation of the virus used formalin in a concentration of 5 percent with respect to the overall volume of vaccine.

In Switzerland, Graub, Zschokke, and Saxer used 0.3 percent solution of crystal-violet dye for inactivation of the virus in order to obtain vaccine.

In Italy, Vianello used anisol (methylene ether of phenol), which inactivates the virus without destroying its antigenic properties, for the same purpose.

According to Maitland's data, virus treated with a 2 percent

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solution of phenol (pH 7.4) at 26 degrees Centigrade for 24 hours or at 37 degrees Centigrade for 6 hours loses its activity and at the same time its antigenic properties.

In the English commission's experiments the effect on the virus of acriflavin was determined. It turned out that virus inactivated with acriflavi.. possesses weakly pronounced antigenic properties, and consequently, such vaccine cannot be useful for practical purposes. Janssen, using various methods of adsorption, obtained foot-and-mouth-disease virus in undissolved form, free of bulk albumins. Virus in such form, in the author's opinion, can be used as a vaccine.

Vallee and Bridre, and later Vallee and Carre, succeeded in accomplishing inactivation of the virus by means of the reaction on it of monovalent hyperimmune serum and in obtaining sensitized virus by this means. In an experiment on 27 head of cattle with intradermal injection of sensitized virus, completely satisfactory results were obtained. Unfortunately, these interesting data were not later tested by anyone, and the authors themselves did not continue their investigations.

Aliverdiev (1945), in experiments on cattle, tested sensitized virus which they had obtained by means of treatment of the latter with convalescent serum as an antigen for active immunization against foot-and-mouth disease. He treated the finely ground epithelium of aphthae with convalescent serum from sick animals. After this he added to the prepared mixture 0.2 percent of commercial formalin and shook it up thoroughly. The mixture of serum and virus was left in a dark

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place for 48 hours. The sensitized virus was injected into animals intracutaneously in the region of the cheek in a quantity of 0.5 cubic centimeters. In an experiment on 60 head of cattle Aliverdiev obtained completely satisfactory results; however, he refrained from any conclusions until after the performance of experiments under practical conditions.

Nuelaux, Ninjard, and Cordier used the method of biological attenuation by means of symbiotic cultivation of foot-and-mouth-disease virus and smallpox virus from sheep for obtaining anti-foot-and-mouth-disease vaccine; however, the authors did not draw any conclusions from their experiments.

Belen prepared a special "aphthous-vaccine complex", consisting of foot-and-mouth-disease virus and smallpox virus (vaccine), which had first been inactivated by heating at a temperature of 60 degrees or treated with 2 percent solution of iodine. The author carried out large-scale experiments in this direction, but the results of his experiments were unsatisfactory.

Waldmann and Keppin attempted to attenuate the foot-and-mouth-disease virus by means of cultivating it in tissue media in the presence of living tissues, but the experiment showed that simultaneously with attenuation of the virulent properties of the virus its antigenic properties also decrease. Virus attenuated by this means proved unfavorable for purposes of immunization.

All attempts to accomplish attenuation of the virus by means of adaptation of the latter by means of passages in various types of animals must be considered unsuccessful so far, although in theory it is impossible to deny the possibility of biological modification of it in the sense that this could occur, for example, with smallpox.

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FORMOLÉ-VACCINE

As early as 1925, Vallee, Carre, and Rinjard proved with their investigations that a state of active immunity may be caused in cattle with the help of subcutaneous injections of definite quantities of virus treated with formalin. At first they prepared formolé-vaccine from the virulent blood of sick animals. However, such vaccine possessed relatively weak antigenic properties, and it was necessary for immunization of animals to inject it in large amounts.

Upon using virus in the form of the epithelium of the severing of a foot-and-mouth disease vesicle for the same purpose, the vaccine was more active. With small doses injected subcutaneously it caused the formation of immunity in cattle. In France, Richart inoculated 6,845 head of cattle with the method of Vallee, Carre, and Rinjard, completely satisfactory results being obtained.

In the USSR, my associates and I (Lavrovskiy, Popova, Krasovskiy, Babich, Lipatov), and likewise other investigators (Yuskovets, Savel'yev, Mirotvorskiy) and veterinary doctors and practical workers (Maslov, Kostyuchenko, Lomakin, Sil'chenko, and others), have at different times inoculated 7,699 head of cattle with formolé-vaccine. Cattle numbering 2,697 head have been inoculated subcutaneously by the method of Vallee, Carre, and Rinjard, and using our method, i.e. intracutaneous inoculation, we have inoculated 3,888 head once and 1,094 head twice. These experiments have confirmed the data obtained earlier by Vallee,

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Carre, and Rinjard with respect to the possibility of achieving immunity to foot-and-mouth disease in cattle by means of using virus treated with formalin.

Proceeding from the special sensitivity to the virus of cells of the dermal tissue and the dermatropic nature of the virus, we have reckoned that intracutaneous immunization to foot-and-mouth disease is just what gives the most stable and prolonged immunity. Our reasonings on this question, expressed on the basis of preliminary experiments, have received support on the part of Vallee, and also of Bezredka, and later, in subsequent investigations, Soviet as well as foreign, have found complete confirmation.

As to the question of the duration and nature of immunity in cattle, various investigators have obtained non-uniform results. In our experiments we have not been able to verify the occurrence of complete immunity after immunization with formolé-vaccine. With control infection of vaccinated animals a primary aphtha developed on the site of application of the virus, but generalization of the infection, however, did not set in, i.e. the animals acquired only humoral (relative) immunity. Our experimental results coincide completely with the data of Bedson, Maitland, and Burbury, who performed their investigations on guinea pigs.

With respect to the speed with which immunity sets in following vaccination, data are likewise sharply divergent.

Vallee, Carre, and Rinjard consider that immunity sets in rather slowly after vaccination. Investigations by the author

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and his associates, on the other hand, have shown that immunity sets in rather rapidly after vaccination. Bedson, Maitland, and Burbury also came at one time to similar conclusions with respect to the speed with which immunity sets in, on the basis of experiments performed on guinea pigs.

After inoculation of cattle with formolé-vaccine, immunity evidently occurs no longer than 1.5 to 2 months. Richart asserts that immunity in animals after vaccination lasts no less than 3 months. Vallee, Carre, and Rinjard do not insist on such a prolonged immunity, since in their experiments they performed tests on only the 26th, 31st, 34th, 36th, 48th, and 50th days following vaccination.

In our experiments immunity was constrained to a range of 32 to 48 days, following which individual cases of foot-and-mouth sickness began to appear in the vaccinated herd.

Bedson, Maitland, and Burbury succeeded in immunizing guinea pigs by means of intramuscular injection of formolé-vaccine. In this case a state of immunity set in rather rapidly after vaccination, but immunity was not complete -- only relative. A test of immunity was performed by the authors by means of intradermal infection of guinea pigs in the plantar surface of the rear extremity. To test immunity they used a rigidly determined quantity of virus (20,000 minimal doses). Experiments of no less interest on immunization with formolé-vaccine were carried out in Holland by Monteil. He succeeded with Vallee, Carre, and Rinjard's method in

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immunizing not only guinea pigs, but also swine. (Vaccine was prepared in the following manner: 1 cubic centimeter of virulent "lymph" of a guinea pig or pig was diluted in 49 cubic centimeters of physiological solution of sodium chloride, then formalin 1:1000 was added to this solution, and finally all this was kept in a thermostat at temperature 28 degrees Centigrade for 48 hours.)

Guinea pigs were injected with vaccine subcutaneously in the amount of 0.1 to 0.5 and 1 cubic centimeters, once or twice, with intervals of three to seven days. In ten days following vaccination a test was performed for the presence in them of immunity, by means of intramuscular, subcutaneous, or cutaneous injection of 0.01 cubic centimeters of virulent "lymph". The guinea pigs which had been injected with 1 cubic centimeters of formolé-vaccine possessed sufficiently stable immunity against artificial infection.

Still more interesting results were obtained by Monteil in vaccinating swine. In one instance 50 pigs were used for the experiment, of which 37 head were vaccinated and 13 left as control animals. The vaccine was injected subcutaneously in an amount of 12 cubic centimeters. In another case there were 40 pigs in the experiment, on which 30 had been vaccinated and 10 left as control animals. Formolé-vaccine was injected subcutaneously in the amount of 25 cubic centimeters. In 8 days following the inoculations of vaccine both herds were exposed to control infection, one portion of the experimental animals being injected intravenously with 0.25 cubic centimeters of the contents of foot-and-mouth disease vesicles

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("lymph"), and the other portion of the experimental animals being left under conditions of natural infection.

As a result of the control tests, the 37 pigs vaccinated in the first experiment 13 (35 percent) remained healthy, and the remainder became diseased. Of the 13 unvaccinated pigs, 9 became diseased and 4 remained healthy. Of the 40 pigs vaccinated in the second experiment, 21 (70 percent) remained healthy. Of those which were not vaccinated, 8 became diseased and 4 remained healthy. Montsil came to the conclusion that with inoculations of formolé-vaccine it is possible to achieve a rather stable immunity, but that for this it is necessary to inject large doses of vaccine. Thus, on the basis of fairly numerous experimental data it may be considered proved that there is a possibility of immunization against foot-and-mouth disease with virus which has been killed with formalin. (The question as to whether formalin in the concentrations indicated kills the virus must be considered unproved. It is possible, as several investigators suggest, that "formalin changes its activity, and condenses the albuminal tissue medium in which the virus is located". Therefore, in this case it would be more accurate to speak not of "killed" but of "inactivated" virus, which is so far debatable, however.)

Waldmann, on the basis of his experiments and of Helm's experimental data, long denied the possibility of the occurrence of immunity upon immunization with formole-vaccine.

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At the Eleventh International Veterinary Congress in London, Waldmann made the following declaration à propos of this question: "Unfortunately, we have not succeeded in achieving in our experiments the good results obtained in practice by Vallee and his associates, and also by Skomorokhov ..., but nevertheless we believe in the possibility of active immunization".

Waldmann, Köbe, and Pyl published in 1937 new data from their experiments in the field of active immunization, wherein they had used formolé-vaccine as an antigen. Experiments which they performed on guinea pigs showed that 100 percent of these animals acquired immunity upon inoculation with formolé-vaccine. Positive results were also obtained by the authors upon immunization of cattle with formolé-vaccine. It is easiest to immunize young stock, as the most susceptible to foot-and-mouth disease, with vaccine prepared from virus in the form of the epithelium of the walls of cattle aphthae by means of treating it with formalin, 75 percent of stock so vaccinated remaining resistant to foot-and-mouth disease upon direct contact with sick animals. In animals inoculated with formolé-vaccine immunity develops, as a rule, toward the 14th day and lasts for 3 or 4 weeks. Inoculation with formolé-vaccine does not involve a clinically visible reaction, and in particular, a rise in temperature.

Under experimental conditions, Syurikov and Golubev vaccinated pigs with virus attenuated with formalin, recommended by certain investigators (Savel'yev and others) for artificial infection on

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contaminated farms. They injected the formalinized virus under the skin, in adult pigs in quantities of 1 cubic centimeters, and in young pigs up to 2 months and older in quantities of 0.2 cubic centimeters. The adult pigs underwent the inoculation relatively easily with an inconsiderable increase in temperature on the 5th to 7th day (at 0.5 degrees Centigrade). Sucking-pigs 8 to 10 days old became diseased and died following inoculation on the 10th day. In this case the investigators were dealing with attenuated virus, but virus which had not lost its virulence, and therefore all inoculated animals developed foot-and-mouth disease -- adults in mild form and sucking-pigs in malignant form.

As material for the preparation of formolé-vaccine all the investigators used virus taken in the form of epithelium from the coverings of well-developed, but not yet ruptured, aphthae.

For preparation of formolé-vaccine Vallee, Carre, and Rinjard recommend using virus from the epithelium of the coverings of aphthae from cattle, where it is contained in greatest concentration. After collection of the virus they advise treating it immediately or at least preserving it, or finally, leaving it, simply in the form in which it was collected, in a refrigerating compartment at temperature of 0 degrees Centigrade (of course it is possible to keep the virus in the frozen state, too).

Bedson, Maitland, and Burbury in their experiments used virus from just-developed unruptured aphthae, and also from the coverings of epithelium of 24-hour aphthae of the guinea pig, and finally, from virulent serum.

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For preparation of the formolé-vaccine my associates and I used exclusively virus from cattle in the form of epithelium of the coverings of just-developed, unruptured aphthae. Waldmann, Köbe, and Pyl used as the basis of their experiments the same method of preparation of the vaccine they used virus from cattle in the form of the epithelium of just-developed 24-hour aphthae. In preparing formolé-vaccine from virus from a guinea pig these authors used epithelum and contents of aphthae. In addition, Waldmann, Köbe, and Pyl prepared formolé-vaccine from virulent blood and serum obtained in 30 hours from a guinea pig specially infected for this purpose.

According to Vallee, Carre, and Rinjard, virus collected for preparation of vaccine in the form of the epithelium of aphthae is first weighed, cut up slightly for the purpose of maximum division, and then ground thoroughly in a mortar with a small quantity of physiological solution of sodium chloride and sand (the latter is added for better grinding of the epithelium). To the emulsion obtained after grinding of the epithelium is again added a certain amount of the same physiological solution, and then all this is filtered through a very fine cloth. The mass remaining on the filter is again rinsed several times with the physiological solution so that for every 0.3 grams (one inoculatory dose) of epithelium of the coverings of aphthae there would be 10 cubic centimeters of physiological solution of sodium chloride. For testing the virulence of the prepared virus a group of guinea pigs are infected. Following this to the liquid ("suspension" of virus) is added 0.2 cubic centimeters of 1:4 water solution of

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ordinary formalin; the mixture is shaken up well and then kept for 48 hours in a warm place at ordinary room temperature (16 to 18 degrees Centigrade). After the designated interval the formolé-vaccine is tested for sterility by infection of guinea pigs, and only then can it be released for use.

Bedson, Maitland, and Burbury first diluted aphthous virus in the proportion of 1:50 (M/50) with a buffer solution of phosphate (pH 7.6). The activity of the virus was tested on guinea pigs by means of intradermal infection in dilution of 1:5,000,000. Virulent serum was obtained from the blood of guinea pigs following preliminary defibrination of the blood. The epithelium was ground with sterile sand, after which 20 parts of M/50 buffer solution of phosphate were added for every weight unit. To free it from suspended particles, the virus thus obtained was centrifugated, and then formalin in the proportion of 0.1 percent was added to the liquid containing the virus. After this the mixture was placed in a thermostat at 26 degrees Centigrade for 48 hours. For intensification of the antigenic action of the vaccine Bedson, Maitland, and Burbury injected inoculated animals intramuscularly with 0.1 cubic centimeters of normal guinea pig or rabbit serum (also treated with formole-vaccine), 1 percent solution of casein in the amount of 1 cubic centimeter, or anti-cattle-plague vaccine in the amount of 0.25 cubic centimeters.

Waldmann, Köbe, and Pyl in general treated the virus in just the same manner as did the English investigators. They diluted

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the virus with 1:50 M/15 buffer solution of phosphate (pH 7.6). In some instances, one quarter of the volume of the phosphate-buffer solution was diluted with normal guinea pig serum. Formalin was then added in concentration not of 0.1 percent, but of 0.15 percent, which according to Waldmann, Kübe, and Pyl does not affect the active properties of the vaccine, whereas it reliably kills foreign microorganisms in the vaccine. The vaccine was placed in a thermostat for 24 hours at 25 degrees Centigrade. Virulent serum was obtained for their experiments by Waldmann, Kübe, and Pyl from guinea pigs 30 hours after infection. To it was added 0.15 percent formalin and then it was placed for 48 hours in a thermostat at 25 degrees Centigrade.

According to Bedson, Maitland, and Burbrury's data, 10 times less virus is contained in the serum of sick animals than in the "lymph" of foot-and-mouth disease aphthae, but formolé-vaccine prepared from it also possessed well-pronounced immunizing properties.

For purposes of studying the influence of immune serum on the immunizing process caused by formolé-vaccine, Bub injected guinea pigs simultaneously with formolé-vaccine and immune serum. Upon injection of increasing quantities of serum he established that the process of active immunization was inhibited. The antibodies of the serum, so he supposes, "neutralize" the formolé-vaccine. Consequently, active immunization (simultaneous inoculation). Under such conditions, as Bub's investigations showed,

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active immunization of the system does not take place. As Bub points out correctly, it is possible that the various results of the application of formola-vaccine stem from the fact that it, although obtained by one and the same method and under the same conditions of the external medium, nevertheless possesses non-uniform and inconstant immunizing properties.

Khomutov established that in treating virus with formalin in dilution of 1:1000 at 20 degrees Centigrade, without the admission of light, it loses its virulence in 48 hours, at the same time keeping its antigenic properties for a time up to 8 days. Virus treated by the same method and kept at 20 degrees Centigrade for 48 hours, and then in a refrigerating compartment at 2 degrees Centigrade, stayed virulent for 19 days, and its antigenic properties were preserved for 26 days. Virus ("lymph") in a preservative glycerine medium (pH 7.6) in dilution of 1:100 kept its virulence for 17 days and its antigenic properties for 79 days upon the addition of formalin in the proportion of 1:1000 at 20 degrees Centigrade without the admission of light.

Khomutov also studied the virucidal effect of various concentrations of formalin (0.5:1000, 1:2000, 2.5:1000, and 5:1000) in the presence of chloroform. Taken in the amount of 1 percent to the overall volume of formalinized virus diluted with phosphate-buffer solution, chloroform attenuates the virucidal action of formalin on the virus. In treating the virus with formalin in the ratio 0.5:1000 and chloroform in 1:100, it being stored for 48

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hours at 20 degrees Centigrade and then in a refrigerating compartment at 2 degrees Centigrade, it kept its virulence for 19 days and antigenic properties for 25 days. In treatment with formalin in the ration 1:10,000 and chloroform in 1:100 and with storage at 20 degrees Centigrade for 48 hours, virulence was preserved for 7 days and antigenic properties for 19 days. With the same treatment of the virus and the same storage of it at 20 degrees Centigrade for 48 hours and then in a refrigerating compartment at 2 degrees Centigrade, it kept its virulence 17 days and antigenic properties 12 days.

Khomutov's experiments, as may be seen from the attached data, offer very great interest and cannot go unheeded in the development of methods of inactivating the virus. On the basis of data of French, Soviet, English and German investigators it is possible to consider conclusively proved the possibility of active immunization with virus inactivated by means of various concentrations (0.1 to 0.15 percent) of formalin.

Immunity resulting from the injection of formolé-antigen (formolé-vaccine) is incomplete (relative). However, with the help of further modification in the vaccine itself as well as in the technique and method of inoculations the duration and stability of immunity may be increased. (The aluminum-hydroxide vaccine of Danish investigators, somewhat modified by Waldmann and Köbe, offers the most highly-perfected version of formolé-vaccine, being

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the result of further development of methods of active immunization based on the use of virus inactivated (or killed) with formalin as an antigen.)

In experiments of Soviet investigators (Skomorokhov and others) and also of German investigators (Waldmann, Köbe, and Pyl) the intracutaneous method, and in the experiments of English investigators (Bedson, Maitland, and Burbury) the intramuscular method, have given the most effective results. The possibility of active immunization with formolé-antigen must be considered conclusively proved with respect to the guinea pig (Bedson, Maitland, and Burbury), cattle (Vallee, Carre, and Rinjard; Skomorokhov; Waldmann, Köbe, and Pyl; Schmidt, Hansen, and Schmit-Jensen; Savel'yev and others), and swine (Monteil).

Animals susceptible to foot-and-mouth disease can be a source for obtaining virus material for the preparation of vaccine -- cattle, swine, and guinea pigs, from which virus is collected in the form of the epithelium of the coverings of well-developed, but not yet ruptured or just-ruptured, aphthae. Evidently virulent blood may also be used for preparation of vaccine, the blood being taken from sick animals with high temperatures. Finally, the possibility is not excluded of using cultured virus for preparation of the vaccine, although experiments performed in this direction at the Riems Institute have so far produced negative results. Further scientific research is needed in this direction, in order to make formolé-vaccine an easily-accessible and inexpensive method of the practical combat against foot-and-mouth disease.

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DANISH ALUMINUM-HYDROXIDE VACCINE

An original method of preparing anti-foot-and-mouth-disease vaccine was developed in 1934 by the Danish investigators Schmidt, Hansen, and Schmit-Jensen. The basis of this method is the principle of adsorption of the virus by means of aluminum hydroxide; this principle is borrowed from the works of the Danish investigators Schmidt, Jensen, and Nilsen, who were the first to use it for obtaining antitoxin serums.

The virus, as shown by investigations, loses its virulent properties in 24 to 48 hours in the presence of aluminum hydroxide at 37 degrees Centigrade, but keeps well-defined antigenic properties. As virus material for the preparation of vaccine the investigators used foot-and-mouth-disease virus from 24-hour aphthae of guinea pigs and serum containing the virus.

The method of preparing the vaccine is itself summarized as follows. The virus, prepared in the form of a 2 percent suspension, is mixed after preliminary centrifugation in proportion of 4:6 with aluminum orthohydroxide in the modification prepared by Wilstetter. At first a monovalent vaccine was prepared from type O virus (after Vallee). Experiments were performed on guinea pigs.

In testing immunity in 7 days following vaccination by injecting 10,000 virulent doses of virus, the presence of immunity was established in the guinea pigs inoculated with vaccine. After this the experimenters prepared a plurivalent vaccine from equal portions aluminum-hydroxide-treated type O, A, and C virus. The vaccine was injected in experimental guinea pigs in a quantity of 0.1 to 1 cubic-centimeters. In 12 days the presence of a rather stable immunity was

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established in all the experimental animals.

In addition, the experimenters attempted by means of adding aluminum hydroxide to the formalinized virus in the ration 20:100 to intensify the immunizing action of the formole-vaccine, which was not verified, however, upon testing the immunity.

With two-fold inoculation of guinea pigs, the first time with formole-vaccine and the second time, in 5 days, with virus adsorbed by aluminum hydroxide, the presence of stable immunity was established in the experimental animals. Virus-containing serum used for preparation of vaccine proved sufficiently effective and in any case no worse than virus ("lymph") treated with aluminum hydroxide for 48 hours at 37 degrees Centigrade. In the opinion of the authors, the results of the experiments depend greatly on the degree of virulence of the virus used in preparation of the vaccine.

Aluminum-hydroxide vaccine prepared according to the method of the Danish investigators possessed high immunizing properties. The basic shortcoming of this vaccine consisted in that it was not free from active "living" virus capable of causing foot-and-mouth-disease sickness in animals inoculated with the vaccine, particularly in highly sensitive ones. With the passage of time certain changes have been introduced in the method of preparing the vaccine, which have made it completely suitable for practical purposes.

The work of the Danish investigators Schmidt, Hansen, and Schmit-Jensen has played an outstanding role in the solution of the problem of active immunization against foot-and-mouth disease. (The investigators designated were the original authors of the method of aluminum-hydroxide vaccine, and Waldmann and Kobe can claim authorship of only the part embodying the perfections which they introduced in the method

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of the Danish investigators.)

THE ALUMINUM-HYDROXIDE VACCINE OF WALDMANN AND KOBE

Waldmann and Kobe introduced into the method of the Danish investigators certain changes which made aluminum-hydroxide vaccine against foot-and-mouth disease completely suited to practice. As a supplementary component for preparing the vaccine they used a glycol buffer with pH-9 value and formalin in 0.05 percent concentration with respect to the overall volume of vaccine. (It would be more correct to call such vaccine formole-aluminum-hydroxide.) As the result of modifying the method of preparation the vaccine became avirulent, sterile, and harmless, at the same time keeping its antigenic properties, and produced positive results under working conditions. With cattle it was used subcutaneously in a quantity of 15 to 60 cubic-centimeters, with sheep and swine in a quantity of 0.2 to 5 cubic-centimeters, depending on the animal's weight.

Following inoculation immunity developed on the 5th day and reached its maximum on the 14th day. The length of duration of the immunity was an average of 4 to 5 months and longer. In approximately one third of the vaccinated animals a slight increase in temperature was noted (of 1 to 1.5 degrees), lasting no more than 24 hours. The vaccine, according to Waldmann and Kobe's assertion, does not cause any collateral phenomena and does not reflect on the general conditions of the animal. Thoroughbred and pregnant animals undergo inoculation with the vaccine very easily. Vaccinated animals do not give off the virus and consequently are not virus-carriers.

At the XIII International Veterinary Congress in Zurich (1937) Waldmann reported that more than 150,000 head of stock had been ino-

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culated with aluminum-hydroxide vaccine with positive results.

At the IVth International Congress of Pathologists in Rome (1939) Waldmann declared that in Germany the vaccine had been used on 42,472 farms, where more than 500,000 head of stock had been treated, and positive results had also been obtained.

There are also reports from other countries of western Europe on positive results from using aluminum-hydroxide vaccine. In 1939, 30,000 head of stock were inoculated with the vaccine in Switzerland and 12,000 head of stock in Italy. In 1940, in Yugoslavia, 20,000 head of stock were inoculated. Aluminum-hydroxide vaccine was tested in experience with combatting foot-and-mouth disease in Denmark on more than 60,000 head of cattle, and gave good results.

Numerous data obtained on the basis of practical observations demonstrate that aluminum-hydroxide vaccine creates a rather stable and prolonged immunity in almost 100 percent of animals inoculated. The immunity, as a rule, sets in in 8 to 12 days following inoculation and lasts an average of 4 to 5 months. However, Rossi, Schang, and Campion, citing their experiments with vaccination of 2000 head of cattle, 20,000 pigs, and 300 sheep, hold that complete (tissue and humoral) immunity following inoculations usually lasts no longer than 4 months, after which it gradually begins to weaken. And only in individual cases under specially favorable conditions of animal-housing can it last 6 months.

According to Waldmann's report at the XIIIth International Veterinary Congress, up to 1000 liters a week of aluminum-hydroxide vaccine were being produced on the Island of Riems.

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On the Island of Riems virus for preparation of vaccine was obtained from artificially infected calves, in the form of the epitheliun of "fresh", not yet ruptured aphthae. It was possible to collect an average of up to 30 grams of virus material from each calf. The collected material was first weighed, and then ground in an electrically driven porcelain mortar. After this distilled water was added to the ground virus material in such quantity that it contained 7 percent pure virus material. The virus suspension was centrifugated and subjected to filtration.

Each batch usually consisted of a finished measurement of no less than 100 liters of prepared vaccine. For this, 10 liters of virus suspension were used, and mixed with 50 liters of aluminum-hydroxide and 40 liters of glycol buffer solution (the pH of this mixture should be equal to 9), and then formalin was added in quantity of 50 cubic-centimeters (0.05 percent). All this was mixed for one hour in special automatic machines and poured out into liter bottles. The "semi-finished" vaccine was placed in a thermostat for 48 hours at 25 degrees Centigrade. Following, it was kept in a refrigerator at 3 to 5 degrees Centigrade and simultaneously tested for sterility, virulence, and immunogenic properties.

Every deliberable batch of vaccine was tested for harmlessness and suitability for practical purposes on cattle. For this purpose, 4 head of cattle were inoculated, with the observance of all precautionary measures; in 7 days following inoculation the cattle were subjected to a control test for the presence of immunity by means of contact infection, and also again by means of applying virus to the mucous membrane of the tongue for the purpose of artificial infection. The vaccine was considered suitable for practical purposes if after this

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the animals remained healthy.

In the USSR in 1937 Ratner and associates (the All-Union Institute of Experimental Veterinary Medicine) began to occupy themselves with mastering the methods of aluminum-hydroxide vaccination. However, instead of mastering the original method of the authors of this vaccine they proceeded along the path of various modifications in the process of preparation of the vaccine itself (substitution of borate buffer for the glycol buffer, introduction of alum instead of ammonium sulfate, sterilization of the aluminum hydroxide under pressure, etc.), which delayed by several years the introduction into practice of the method of active immunization against foot-and-mouth disease.

In 1940, according to Ratner's report, the laboratory for foot-and-mouth-disease study of the institute designated mastered the method of preparing anti-foot-and-mouth-disease vaccine according to the principle of Waldmann and Kobe. "Large-scale experiments to test the effectiveness of the vaccine on 6000 head of stock under the conditions of a practical campaign against an epizootic showed that it is a reliable protective measure.

"The technological process of preparing the vaccine developed by us on a semi-production scale suitable for oblast and inter-rayon veterinary-bacteriological laboratories makes possible the widespread introduction of this preparation into veterinary practice." (Ratner, L. S. "Active Immunization of Stock Against Foot-and-mouth Disease With Aluminum-Hydroxide Vaccine." Vestn. s-kh. nauki. Veterinariya, vyp. I, pages 5-11, Sel'khozgiz, 1941.)

The data obtained by Ratner on the results of the test of the

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immunizing properties of the vaccine under working conditions were reported at the Eighteenth Plenum of the Veterinary Section of the VASKhNIL in Moscow in 1940. In a resolution on the report it was recorded: "The aluminum-hydroxide vaccine based on the method of Waldmann and Kobe with which the VIEV (Ratner and others) have familiarized themselves produced effective results in experimental testing, and also in working experiments. This vaccine, possessing good immunogenic properties, has revealed that it can be kept within a limit of 4 months..."

At the same plenum of the Veterinary Section of the VASKhNIL Doronin (Kazakh NIVI) reported the results of tests of vaccine prepared according to the Danish method with Waldmann and Kobe's modification. In experiments on cattle he established that in 95 percent of animals inoculated a stable immunity is created, which in 12 to 16 days after the inoculations is capable of resisting artificial and natural infection. Inoculated animals do not give off the virus during the post-vaccinal period. The vaccine was applied to cattle in a dose of 50 cubic-centimeters subcutaneously in the region of the dewlap.

At the Kazakh NIVI aluminum-hydroxide vaccine was prepared according to an original method and made up into set consisting of 10 parts of 7 percent virus filtrate, 50 parts of aluminum-hydroxide, and 40 parts of glycol-buffer solution.

Somewhat later appeared the report of Artyukh, Lukashev, Kulesko, and Lysenko, who evaluate differently the results of experiments with the application under working conditions of anti-foot-and-mouth-disease vaccine prepared by the laboratory of the VIEV. They had collected and studied material obtained through experience with inoculations of 75,213 head of cattle, positive results of inoculations being noted in

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only one rayon of five investigated. As a result, they drew the following conclusion: "Aluminum-hydroxide vaccine against foot-and-mouth disease prepared according to Waldmann and Kobe's method, upon mass application of it in the autumn of 1941 in one of the oblasts of the RSFSR, imparted to inoculated cattle a brief and insufficiently stable immunity. Immunity set in slowly--no earlier than the third week following inoculations--and lasted no more than 2 to 3 months, even under the most favorable conditions for the occurrence of non-susceptibility to infection."

Leaving no doubt as to the practical value of aluminum-hydroxide vaccine, these authors suggest that the cause of the insufficient effectiveness of the VIEV vaccine which was applied under working conditions in 1941 is the substantial deviations adopted by the VIEV's laboratory for foot-and-mouth-disease study, departing from the methods of Danish and German authors with respect to dosage of the vaccine, storage conditions, etc., which could not help reflecting on the results of vaccination.

Toussieng reports unsuccessful with the application of aluminum-hydroxide vaccine to calves, pigs, and guinea pigs. With inoculations of vaccine prepared from different strains of virus and applied twice, negative results were obtained. He likewise reports that vaccine used at the present time for active immunization of cattle proves ineffective for swine.

Individual failures in testing the vaccine under working conditions do not in any degree devalue its practical importance. At the present time there should be no question of the effectiveness of aluminum-hydroxide vaccine, which had been completely substantiated scientifically and tested on millions of head of stock in the countries

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of western Europe, but rather of how to make this new preparation accessible and inexpensive in practice.

The technique of preparing aluminum-hydroxide vaccine is still rather complicated, production of it must be kept under strict supervision, and above all it should not be considered that the problem has been solved of cultivating the virus in tissue media in the quantities necessary for the purposes of mass-production of biological preparations.

The French investigator Verge considers that widespread introduction of this method into practice involves great difficulties, specifically: (1) obtaining large quantities of virus, inasmuch as the problem as to the use of cultured virus for these purposes so far remains unsolved, (2) standardization of methods of inactivating the virus, and (3) preparation of vaccine with strictly constant immunizing properties.

There are also statements which associate the practical value of aluminum-hydroxide vaccine with the "static nature" of foot-and-mouth disease.

Minett considers that the vaccine is a very valuable method of combatting foot-and-mouth disease in such countries as Germany, where the disease is static, but completely unusable in England.

CHLOROFORM-VACCINE

The scientific research of Galea, and also of Khomutov in France, with respect to inactivation of the virus opens very interesting prospects in the field of development of new methods of active immunization against foot-and-mouth disease.

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Galea proved, in experimental conditions and using substantial material, that virus treated with chloroform loses its virulent properties, at the same time keeping its antigenic properties.

The chloroform-antigen which he obtained was tested as a vaccine against foot-and-mouth disease. As the result of the experiments it was established that animals inoculated with chloroform-vaccine acquire immunity. As virus material for preparation of chloroform-vaccine Galea used virus from well-developed 24-hour aphthae. The epithelium of aphthae-coverings was first cut up and then ground thoroughly in a porcelain mortar with the addition of a physiological solution of sodium chloride (for every gram of virus used 100 cubic centimeters of physiological solution was added). After this the virus suspension was centrifugated for 30 minutes in order to free it from coarse particles. The upper layer was decanted and then chloroform in the amount of 1 percent was added to the virus suspension. The chloroform-antigen thus prepared was left at room temperature, 16 to 18 degrees Centigrade, in a cabinet without access to the air. It was shaken up several times a day. In 10 days a test for avirulence was performed, the virus as a rule losing its virulence during this time under the influence of the chloroform, but keeping its antigenic properties. If large particles were left in the virus suspension the action of the chloroform proved to be inadequate, and the prepared suspension stayed virulent for as long as 16 to 18 days.

Under the conditions designated the chloroform-antigen kept its immunizing properties for 27 days. The destruction of the chloroform-antigen and such rapid loss of its antigenic properties are explained by Galea by the change in the pH of the medium which is inevitable with storage at a temperature of 16 to 18 degrees. He made the

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observation that even at 4 degrees there takes place a change in the magnitude of the pH of the medium in the direction of acidity. On the other hand, at low temperatures of -8 to -10 degrees, when the chloroform-antigen freezes, noticeable change in the magnitude of the pH of the medium does not occur, and the chloroform-antigen then does not lose its immunizing properties for 5 months. Stored under these conditions for 142 days, it possessed the same immunizing properties as freshly prepared antigen.

The immunizing properties of the chloroform-antigen were checked by Galea only on guinea pigs. Chloroform-antigen was injected intradermally--in nappe--in the region of the belly, in the amount of 1 cubic-centimeter. In later experiments Galea proved that 0.1 cubic-centimeters is sufficient to cause immunity in a guinea pig (0.1 cubic-centimeters of chloroform-antigen corresponds to 1 milligram of virus taken in the form of the coverings of foot-and-mouth-disease vesicles). Testing of the virus was performed by means of intradermal infection (0.5 cubic-centimeters of virus were injected) or subcutaneously (1 cubic-centimeter of virus was injected) from 24-hour guinea-pig aphthae (the minimum quantity of virus capable of causing infection in a guinea pig was 0.5 cubic-centimeters of virus in dilution of 1:50,000). For control purposes, the same number of guinea pigs were used each time as in the experiment. As a result it was established that with intradermal injection--in nappe--chloroform-antigen in the amount of 1 cubic-centimeter causes a rather stable immunity in the guinea pig, lasting up to 5 months. However, the immunity acquired by guinea pigs is incomplete, or in other words, relative, and there-

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fore with control infection on the site of injection of the virus primary aphthae developed on them without subsequent generalization of the infection. (With intradermal infection 500 minimal infectious doses were injected, and with subcutaneous infection 1000 minimal infectious doses.)

In other experiments Galea altered the method of injecting the chloroform-antigen. In order to obtain a more stable immunity he began to perform immunization in two doses: the first time, he injected chloroform-antigen intradermally at several points for the purpose of creating a "defensive zone", and the second time he injected virus intradermally in the center of this zone (no earlier than 4 days after injection of chloroform-antigen). Injection of virus in the "defensive zone" in 24 to 72 hours, as shown by experiments, does not involve the development of a generalized process of infection. With this unique combination injection immunity sets in 6 days after injection of virus into the defensive zone or 10 days after injection of chloroform-antigen. Guinea pigs vaccinated by this method acquired a stable immunity. The inoculated animals prove to be resistant to 8000 minimal infectious doses of virus, while those which are inoculated once without subsequent injection of virus do not possess resistance to such large doses of virus. The blood of vaccinated animals does not contain virus and, when injected in animals susceptible to foot-and-mouth disease, does not cause sickness. Galea expressed the hypothesis that such results may also be obtained with vaccination of cattle.

In the USSR large-scale experiments were performed at one time on the use of chloroform-vaccine on cattle. Preliminary experiments were performed in the Foot-and-mouth-disease Institute

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under our guidance by Peshekhonova and Volkova, who established the presence in experimental animals of immunity acquired in consequence of vaccination. The vaccine was injected into the animals by the intracutaneous method, twice in amounts from 0.2 to 0.5 cubic-centimeters to 1.0 cubic-centimeters. The results of the experiments showed that it is thus possible to achieve satisfactory results with inoculations of cattle under farm conditions.

Later, experiments were performed under conditions of a practical campaign against foot-and-mouth disease, for which three expeditions were organized to study this problem.

During the expeditions Lavrovskiy, Dobrotvorskaya, Rafalovich, Volkov, and others treated 6789 head of cattle with chloroform-vaccine. Immunity was tested at various intervals, under conditions of natural contact as well as by the method of artificial infection. In two groups of experiments (with large numbers--5622 head of cattle and 574 head of young ones) immunity was tested 4 months after vaccination. In a control test, after natural contact with sick animals 73.8 percent of animals from the first group did not get sick, and 96.2 percent from the second group. From the first group 80.5 percent of young animals did not get sick, and 100 percent from the second group. As a control for susceptibility to foot-and-mouth disease 639 head of adult cattle were left uninoculated (96.7 percent of these got sick), and also 314 calves (96.8 percent of these got sick). Thus it was proved that the immunity of vaccinated animals lasts for 4 months, and considerably longer for the overwhelming majority of them.

Rafalovich, for the purpose of determining the practical

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importance of chloroform-vaccine, performed experiments at one of the meat-sovkhozes of East Kazakhstan (1934) on cattle during the pasture period. (Experiments were performed by Rafalovich jointly with his scientific colleagues Lavrovskiy and Dobrotvorskaya.) In the first group of experiments 240 head of cattle were treated with chloroform-vaccine. The vaccine was injected twice by the intracutaneous method, the first time in quantity of 1 cubic-centimeter and the second time in the same quantity and 14 to 16 days later.

In the second group of experiments 122 head of cattle were treated according to the same system, vaccine being injected in smaller quantity--0.05 cubic-centimeters apiece. Two hundred head of cattle were left uninoculated for control purposes. As a result, 34.1 percent of the first group and 69.7 percent of the second group became sick. All unvaccinated stock became sick in 3 to 5 days. However, in the process of clinical observation it was established that in 10 to 14 days after inoculation cases of foot-and-mouth-disease sickness appear among vaccinated animals. Rafalovich explained these cases by the state of short-term immunity caused by intracutaneous immunization. Injection of vaccine in the amount of 0.5 cubic-centimeters is evidently insufficient, which may be seen from comparative evaluation of the first and second groups of the experiment.

Later, he set up a second experiment, in which he used the intracutaneous method in combination with the subcutaneous method. For this purpose 50 head of cattle, inoculated intracutaneously with vaccine by the system used earlier, were treated by means of subcutaneous injection with a double amount of vaccine, i.e., they were injected with 2 cubic-centimeters in 5 days following the second

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intracutaneous inoculation. As a control for this experiment 70 head of cattle from the same herd were used, vaccinated by means of intracutaneous inoculation. In 10 days, upon clinical examination, 2 head of cattle were picked out of this experimental group, suspected of foot-and-mouth-disease sickness (atypical scars at the site of healing of ulcers on the membrane of the upper lip). All of the control stock developed foot-and-mouth disease individually. The experimental stock (vaccinated as well as control) were kept under uniform housing conditions: in pasture during the day, at night in the cattle shed without tether, where there were common feed-troughs, watering-troughs, etc. Thus the vaccinated stock were in close contact all the time with the remaining stock of the entire herd. Through serological examination of experimental stock by the method of the conglutination reaction it was established that antibodies in the blood increased following subcutaneous vaccination.

On the basis of the experiments Rafalovich drew the following conclusion: "chloroform-vaccine prepared according to Galea's method, upon once-repeated subcutaneous injection over a two-week interval of time, creates in cattle an immunity to foot-and-mouth disease lasting no more than 2 weeks. A vaccine-dose of 0.5 cubic-centimeters is insufficient for the creation of even two-week immunity, which sets in only upon usage of vaccine in a dose of 1 cubic-centimeter. The combined method of vaccination, i.e., once-repeated injection of vaccine into the skin and then injection of it under the skin in quantity of 2 cubic-centimeters 5 days after this, creates immunity of no less than 30 days' duration and capable of resisting infection in the closest contact between vaccinated

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animals and foot-and-mouth-disease-infected stock." The experiments performed are considered by Rafalovich as inadequate for conclusive solution of the problem as to the practical importance of chloroform-vaccine, but he points out that this method deserves more thorough study and testing under laboratory as well as working conditions.

In one of the oblasts of the Union my associates and I used chloroform-vaccine under working conditions for the purpose of preventing further development of a foot-and-mouth-disease epizootic. On one contaminated farm with an overall stock-population of 986 head, 873 head of cattle were inoculated and the remaining 113 head were segregated toward the moment of inoculation with clinical symptoms of the disease. As a result of vaccination 62.7 percent of the stock were protected, and further development of the epizootic was checked.

On another contaminated farm with an overall stock-population of 1129 head of cattle, 1039 head were inoculated, and the remaining 90 head were segregated toward the moment of [redacted] inoculation with clinical symptoms of the disease. As a result of vaccination 96.6 percent of the stock were protected. At a point contaminated with foot-and-mouth disease where the stock were housed individually, 174 head were inoculated and 34 head were segregated at the moment of performance of the injections as sick with foot-and-mouth disease.

Over the course of six months' observation there was not a single case of foot-and-mouth-disease sickness among the inoculated animals, with the presence of unliquidated foot-and-mouth disease in the region.

In a suburban rayon of the same oblast, where about 40 percent

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of the whole stock-population were afflicted with foot-and-mouth disease, all remaining stock not afflicted with foot-and-mouth disease (amounting to 5538 head, including 1085 head of young animals, 154 head sick with brucellosis, and 693 with tuberculosis) were treated with chloroform-vaccine by the same authors. In the process of further observation of the inoculated animals, 114 head (2.05 percent) were segregated with a clinically pronounced reaction to the inoculation on the part of their systems: salivation--2.05 percent, specific irritations in the buccal cavity--0.68 percent, refusal of fodder--0.45 percent, decrease in milk production--0.25 percent, loss of weight--0.13 percent, and temperature rise--0.05 percent. No other deviations from normal or complications due to the inoculations were noted. All the designated phenomena were connected with the use of vaccine series No 10, in which the virus was evidently insufficiently inactivated. After continuous treatment of all stock with chloroform-vaccine foot-and-mouth disease in the rayon was halted, and not a single case of foot-and-mouth-disease sickness among the inoculated animals was later recorded.

In another rayon of the oblast we performed vaccination for prophylactic purposes on all farms threatened with foot-and-mouth disease. In all 408 head of cattle were inoculated, only five of those inoculated showing salivation without specific irritations in the buccal cavity and 2 head showing specific, rapidly passing phenomena in the buccal cavity.

In the same year, in another oblast of the Union, Dubyanskiy, Khomenko, and Dobrotvorskaya, and I jointly used chloroform-vaccine under working conditions as a method of combatting foot-and-mouth disease (on farms contaminated with foot-and-mouth disease as forced inoculations, and on farms in the threatened zone for prophylactic purposes). At 20 population points in all contaminated with foot-

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and-mouth disease forced inoculations were given to 2251 head of stock, including 1348 adult cattle and 903 head of young animals. As a result, the following number were protected from foot-and-mouth disease in the ranks of inoculated animals: 85.5 percent of adult stock and 97.4 percent of young animals. At all contaminated points sickness of stock was, as a rule, terminated in 14 days following the first inoculation of vaccine.

At the same time, on farms located on the territory of the threatened zone (123 population points) 11,143 head in all were inoculated for prophylactic purposes, including 8131 adult cattle and 2962 young animals. During the whole period of veterinary observation of the inoculated stock not a single case of sickness due to inoculations was recorded. In individual cases only a slight decrease in milk yield during the first one or two days following the inoculations was noted. (Analysis of the results of chloroform-vaccine inoculations in all rayons was performed by special oblzo commissions with the participation of rayon veterinary doctors, scientific associates of the LenNIVI, chairmen of sel'sovets, chairmen of kolkhozes, and finally, veterinary workers attached to the given population points.)

On the basis of analysis of results, performed by a commission, of vaccination with chloroform-vaccine prepared under our direct guidance, the following conclusion was made:

"1. At all 20 points contaminated with foot-and-mouth disease at which cattle were vaccinated with chloroform-vaccine, foot-and-mouth-disease sickness among inoculated stock was terminated within 14 days after the first vaccination.

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"2. At points in the prophylactic zone chloroform-vaccine in established doses did not cause foot-and-mouth-disease sickness or any other deviations in animals inoculated with the vaccine.

"3. The period of quarantines at points contaminated with foot-and-mouth disease which had been treated with chloroform-vaccine was shortened by comparison with points where the epizootic of disease ran its course naturally. With cattle-shed-quarantine the stock was kept in the barn for 18 days at most.

"4. At points contaminated with foot-and-mouth disease, twice-vaccinated stock did not develop foot-and-mouth disease upon contact with convalescent and sick animals in 79.4 to 100 percent of cases.

"5. At contaminated points, stock from the number of vaccinated animals which did develop the disease recovered without complications."

On condition of correct and precise observation of method of preparing chloroform-vaccine corresponding to control tests of it prior to application under farm conditions, of fulfillment of the prescribed system of storage, and finally, of appropriate techniques of inoculation, chloroform-vaccine can give positive results, as shown by our experiment.

Immunity to foot-and-mouth disease caused by chloroform-vaccine lasts no longer than 4 to 5 months. It may be intensified by a supplementary (booster) dose of vaccine or by injection of attenuated virus following the setting in of immunity. This problem is in need of further study. Immunity sets in very early in inoculated animals: beginning in some animals as early as the 4th day, and in

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the herd as a whole toward the 12th to 14th day following the first vaccination, after which the epizootic is usually curtailed.

Animals inoculated with chloroform-vaccine do not give off the virus in the active state and are completely safe for their surroundings. The milk of vaccinated cows does not contain active virus. This has been proved in experiments in which new-born calves were fed with it.

The experiments on the use of chloroform-vaccine under farm conditions performed by Skomorokhov, Dubyanskiy, and Khomenko, and also Lavrovskiy and Dobrotvorskaya in various rayons of the Union have produced convincing results, making it possible to draw a conclusion as to the positive qualities of this vaccine.

At present, several tens of thousand of head of cattle have been inoculated on the whole in various rayons and oblasts of the Union with positive results.

Chloroform-vaccine (the chloroform-vaccine used by Soviet investigators does not differ in principle from the chloroform-antigen proposed by Galea for the same purpose) in use is in essence virus which has been inactivated by means of chloroform almost to the point of complete loss of virulence. When injected into the systems of animals susceptible to foot-and-mouth disease, chloroform-vaccine caused a fairly stable and prolonged immunity, capable of resisting natural infection.

Virus collected from cattle in the form of epithelium of the coverings of well-developed, but not yet ruptured aphthae served as material for the preparation of chloroform-vaccine. Evidently

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it is also possible to use for this purpose virus from swine, which would considerably simplify and cheapen the cost of production of the vaccine. The method of active immunization with inactivated virus had not yet been freed of a whole series of shortcomings, and it is so far early to speak of introducing it into widespread practice, but it opens up certain prospects in the matter of using active immunization against foot-and-mouth disease.

Kindyakov, Doronin, and Zotova, in an experiment with immunising guinea pigs with chloroform-vaccine, came to the conclusion that the cause of the relatively weak effectiveness of chloroform-vaccine is the inadequately developed method of using it. The lack of the stable temperature conditions under which inactivation of the virus was performed earlier should reflect, in their opinion, under the reaction of chloroform on the constancy of the immunizing properties of the vaccine. The need for obtaining a strictly sterile preparation led the designated investigators to introduce corresponding alterations into the methods of preparing the vaccine, in order to eliminate also this very serious shortcoming of chloroform-vaccine.

As a result of experimental study of this problem in the Kazakh Veterinary Scientific-Research Institute, there were introduced into the method of Galea, used by us in the Union with the slight modifications of the author and his associates, very basic changes which made it possible to obtain vaccine with constant immunizing properties.

Kindyakov, Doronin, Zotova, and Rumyantsev began to use a thermostat temperature of -26 degrees Centigrade instead of room

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temperature of 16 to 18 degrees Centigrade, at which inactivation of the virus had been performed, as more advantageous from the standpoint of creating constant temperature conditions. In order to obtain a sterile preparation they began, instead of centrifugation and filtration through a gauze filter, to centrifugate and filter the virus mass through asbestos plates SF by means of a Seitz apparatus. The modifications which they introduced into the method of preparing chloroform-vaccine made it possible to obtain "a maximally standard and sterile bio-preparation with high immunizing properties."

The essence of the modified method of preparing chloroform-vaccine may be summarized as follows. The coverings (epithelium) of foot-and-mouth-disease aphthae from cattle, collected from the animals in 24 to 36 hours following artificial infection, serve as material for preparation of the chloroform-vaccine; next a 1 percent suspension in physiological solution of sodium chloride with pH 7.6 is prepared; then centrifugation and filtration through asbestos plates SF is performed; and finally, chloroform (pro narcosi) in the amount of 1 percent is added to the filtrate obtained. The virus mass thus prepared is poured out into small bottles, agitated for 60 minutes, and then placed in a thermostat at 26 degrees Centigrade for 3, 4, 5, and 6 days. In addition, the small bottles with the virus mass are again shaken daily for 10 minutes each time. After this the vaccine is inspected for harmlessness, sterility, and immunizing properties. Through testing of the vaccine for avirulence it has been established that at 26 degrees Centigrade under the action of chloroform the virus loses its infectious properties in 72 hours.

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In a control experiment it was also determined that chloroform-vaccine with large periods of inactivation proved to be more effective than vaccine with smaller periods of inactivation (3-day vaccine created immunity in 50 percent of experimental animals, 4-day vaccine in 90 percent, and 5-day vaccine in 100 percent). Upon once-repeated inoculation with chloroform-vaccine-intradermally (1 cubic-centimeter) and subcutaneously (50 cubic-centimeters in 7 days following the first inoculation) it was proved that immunity capable of resisting natural infection was present in the overwhelming majority of experimental animals.

After testing of the immunizing properties of chloroform-vaccine prepared according to the modified method under experimental conditions, experiments were performed under actual conditions. However, the results of testing of the vaccine were more negative than positive: in 21 days after vaccination 67 percent of the inoculated animals became sick upon contact with sick animals, and 75 percent in the control group. The results of these experiments are in direct contradiction to data obtained earlier on the application of chloroform-vaccine. The authors are inclined to attribute these failures to the non-suitability of the antigenic properties of chloroform-vaccine with respect to the causal agent of foot-and-mouth disease provoking an outbreak of epizootic in a given rayon.

... Kindyakov and Zotova engaged in study of the influence of physical factors on the state of activity of chloroform-vaccine. It turned out that storage of chloroform-vaccine at a temperature corresponding to the general requirements for the storage of bio-preparations does not reflect a change in the immunizing properties of the vaccine for three months. Storage of chloroform-vaccine

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at a temperature of 0 degrees Centigrade for 4 to 6 months involved a decrease in its active properties. Three-fold freezing and thawing of chloroform-vaccine affected its immunizing properties to only a slight degree.

Together with the positive results of using chloroform-vaccine on cattle, unsatisfactory results have also been obtained in individual cases.

Nikolayenko in the Omsk oblast treated 2000 head of cattle with chloroform-vaccine which he had prepared; of these 620 head were inoculated at a point contaminated with foot-and-mouth disease and 1380 head in a threatened zone for prophylactic purposes. The animals were vaccinated twice, with a 6-day interval between the first, intracutaneous inoculation and the second, subcutaneous inoculation. As a result, 159 head (7.95 percent) became sick with clinical symptoms close to the natural forms of foot-and-mouth disease; in 1033 head (51.65 percent) small, single, quickly disappearing (in one to two days) aphthae, with no salivation, were discovered on the mucous membrane of the buccal cavity; and in only 808 head (40.4 percent) were no visible clinical symptoms established.

Inoculations of chloroform-vaccine were performed on farms under conditions completely different from the standpoint of the epizootic situation. However, this did not prevent Nikolayenko from regarding all inoculated animals, on contaminated farms as well as farms free of foot-and-mouth disease, as a homogeneous group of stock in his experiments. For this reason he divided all the animals into three groups according to the degree of reaction, regardless of the epizootic situation on the farm. Actually it was

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not necessary to divide the inoculated animals into three groups, since the presence of single aphthae in the buccal cavity of inoculated animals made it obligatory to consider them as sick and "spreaders" of infection. In Nikolayenko's experiments there were 58.6 percent with the clinical picture of the disease, and such results, naturally, cannot be recognized as satisfactory.

Such "unconsoling" results did not prevent Nikolayenko from drawing the conclusion that "the method of active immunization of cattle with chloroform-vaccine on farms contaminated with foot-and-mouth disease is an extremely desirable measure." He draws a more cautious conclusion with respect to the use of it for practical purposes on farms threatened with foot-and-mouth disease, inasmuch as part of the vaccinated animals (in the author's experiments, 7.95 percent) become sick with a typical form of foot-and-mouth disease, and the sick animals become a source of the spread of infection.

It is completely obvious that the chloroform-vaccine prepared by Nikolayenko was not free of virulent particles of virus due either to purely technical errors or inadequate and incomplete inactivation of the virus, which brought about the development of foot-and-mouth disease by part of the inoculated animals.

Lavrovskiy, Kindyakov, and Doronin, in an experiment with the vaccination of cattle with chloroform-vaccine performed at one of the meat-and-dairy sovkhozes, did not obtain "definite positive results." They attempted by means of this experiment to solve simultaneously a whole series of basic problems of immunization against foot-and-mouth disease: "the periods of advancing immunity,

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its length of duration in inoculated animals, the system's reaction to the injected chloroform-vaccine". As experimental animals they used stock of varied immunobiological resistance, (in the experiment there were as many as 36.7--50 percent of animals with natural resistance to foot-and-mouth disease.) and the test of immunity was performed selectively on small groups (7--10 head) of stock, which distorted still further the true picture of the experiment. Moreover, the basic experiment was tried on a tubercular herd (90 head), and the young animals used for the experiment (from 1.5 to 2.5 years of age) proved to be infected in the process of the experiment due to insufficient inactivation of virus used in preparation of the vaccine.

In a preliminary test for avirulence of the vaccine performed on cattle, the first batch of vaccine caused foot-and-mouth-disease sickness in one bull. Consequently, it contained a considerable amount of virulent particles and, in spite of this, was allowed to be used for active immunization of the experimental animals. A whole series of other errors in method were allowed in the experiment, which completely destroyed its significance.

NIKOLAYENKO'S CHLOROFORM-SAPONIN VACCINE

In 1940 Nikolayenko, in quest of an original vaccine against foot-and-mouth disease, suggested chloroform-saponin vaccine. There was essentially nothing "original" in the vaccine which he proposed, since it was the same as chloroform-vaccine except that saponin had been added to it [redacted] in the proportion used in preparation of malignant-anthrax saponin-vaccine (after Mazzucchi). Nikolayenko's vaccine created a great stir in 1940--41, and some veterinarians were

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ready to see in it the solution of the foot-and-mouth-disease problem.

According to the report of a special commission (Nikolayenko, natner, and others), in experiments performed on cattle the chloroform-saponin vaccine supposedly gave completely satisfactory results. However, numerous data obtained from veterinarians who had used Nikolayenko's vaccine, and repeated tests by the commission under experimental conditions, showed that this vaccine was the product of the non-serious, non-scientific solution of such an important problem as vaccination against foot-and-mouth-disease. According to Terent'yev's report, "Nikolayenko's anti-foot-and-mouth-disease chloroform-saponin-vaccine had neither a theoretical nor an experimental foundation and all of the author's work may be summarized as crude empiricism". (Terent'yev, P. A. "On the 'Scientific' Creation of Professor N. F. Nikolayenko (Touching the History of Anti-foot-and-mouth-disease Chloroform-saponin-vaccine)". Veterinariya, No 1, 1946, pp. 22--26.)

Incidentally, Galea used "saponinized foot-and-mouth-disease virus" for the same purpose as early as 1932; however, negative results were obtained. In testing immunity in 20 days after inoculations all experimental guinea pigs developed foot-and-mouth disease with phenomena of generalization of the infection. Consequently, Nikolayenko's experiments with chloroform-saponin-vaccine were the result of simple ignorance of modern scientific literature.

Kindyakov performed a whole series of special experiments to test Nikolayenko's vaccine, and established that chloroform-saponin-vaccine prepared by his method does not create immunity in inoculated animals, and the addition of saponin to chloroform vaccine deprives it of active properties.

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In 1940 Nikolayenko himself performed inoculations of chloroform-saponin vaccine for prophylactic purposes on one of the large kolkhozes in the Ukraine, which brought about mass, simultaneous development of foot-and-mouth disease on the part of the entire inoculated herd. The vaccine, as it turned out, was not prepared from inactivated virus, but, on the contrary, as we established, contained active virus which had caused an outbreak of foot-and-mouth disease following the inoculations.

CRYSTAL-VIOLET VACCINE

Crystal-violet vaccine was used on a large scale in Switzerland in 1938-1939 (Graub, Zschokke, and Saxer). Blood from animals sick with foot-and-mouth disease, which had at the same time been fortified with virus from aphthae of the same animals, was used as virus material. The blood was taken from the animals during the period of high temperature (no lower than 40 degrees Centigrade [redacted]). With complete draining off of blood, it was possible to obtain up to 20 liters from a single animal. This was enough for preparation of 200 doses of vaccine (the virus material was collected from a slaughtering center in the city of Berne).

The blood obtained from animals was mixed and defibrinated for 20 minutes. Inactivation of the virus was accomplished by means of crystal-violet dye. After addition of 0.3 grams of crystal-violet in the form of a solution (30 cubic centimeters of crystal-violet solution for every liter of blood), the blood was placed in a thermostat for ten days at a temperature of 38 degrees Centigrade [redacted] for complete inactivation of the virus. After this, every bottle of vaccine was tested for

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sterility. For the purpose of increasing the antigenic properties of the vaccine the authors developed a method of enriching it by means of using virus from the epithelium of aphthae.

The vaccine was injected subcutaneously, in the amount of 100 cubic centimeters for each adult animal. The animals vaccinated acquired a relative immunity, sufficiently strong under the conditions of natural infection. However, such immunity can be overcome under conditions of the reaction of superinfectious doses of virus on an animal's system.

In the Berne canton of Switzerland alone, 12,241 animals on 1119 farms were treated with crystal-violet vaccine. Inoculations were also performed in other cantons. In the course of observation of the inoculated animals for 5 to 6 months it was established that there were 0.62 percent of postvaccinal cases of disease and 0.17 percent of cases of disease due to a natural source of infection. After the inoculations, immunity developed toward the 14th day, but the protective effect of the vaccine began to manifest itself as early as the 5th day after vaccination. The duration of the immunity has so far been studied for a limit of 3 months.

In the process of performing mass inoculations with crystal-violet vaccine, as may be seen from the reports of Frei, and also Fluckiger, there were individual failures, but these were apparently due to other causes and were not connected with the antigenic properties of the vaccine itself.

The possibility of using a large amount of virus-blood from animals which have foot-and-mouth disease, and the ease of the method

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itself of preparing crystal-violet vaccine, should attract the attention of investigators in other countries toward the study of the antigenic properties of this vaccine and testing of it under conditions of the practical campaign against foot-and-mouth disease.

ANISOLE VACCINE

Vianello used virus inactivated with anisole as a vaccine. The antigenic properties of virus inactivated with anisole, according to the author's assertions are preserved better than when it is treated with chloroform or formalin. In 1939, anisole vaccine gave very good results (100 percent) against foot-and-mouth disease in his experiments. The experiments were performed on 726 head of cattle. Immunity sets in as little as 10 days following inoculation, and its duration is no less than after inoculation with Waldmann and Kobe's aluminum-hydroxide vaccine.

The method of preparing anisole vaccine consists of the following. Take a 1 percent suspension in distilled water of well-divided epithelium from the coverings of foot-and-mouth-disease aphthae of cattle and filter through a fine tissue; then, add to this mixture a 50 percent water solution of aluminum oxide (after Wilstetter) and glycol-buffer solution to keep the reaction of the medium at a level of pH=9. To inactivate the virus, add to the prepared mixture 0.3 percent of anisole (phenol methylen-ether), and then place all this in a thermostat at temperature of 32 degrees Centigrade for 6 days. The finished vaccine is kept at a temperature of 2 degrees Centigrade. (The method of preparing anisole vaccine is described in detail in the magazine "Clinica Veterinaria", No 17, 1939, pp. 583-613.)

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LIGNIERES' METHOD

J. Lignieres (Argentina) has developed a rather original method of active immunization, which in essence is a unique method of serum vaccination. For this purpose, instead of injecting vaccine a preliminary immunization is performed by means of intracutaneous and subcutaneous injection of anti-foot-and-mouth-disease serum in order to create an "immune field". After this vaccine is injected in the "immune field", in order to develop a more or less stable immunity it was necessary to perform the vaccination three times.

After the death of J. Lignieres further study of this problem was continued by R. Lignieres, who simplified considerably the technique of such vaccination and made it more feasible for practice. (J. Lignieres reported on the results of his experiments as early as the International Veterinary Congress in London, but at that time his report did not produce the due impression.) According to a report of R. Lignieres, it is possible by means of once-repeated vaccination of animals to achieve a sufficiently stable immunity last up to 9 or 10 months.

The new technique developed by R. Lignieres consists of the following. Into the skin of the neck on the right-hand side, or at the base of the ear, is injected 1 cubic centimeter of polyvalent anti-foot-and-mouth-disease serum, and the same quantity of this serum at the same point but under the skin. Into the zone thus immunized, no farther than 4 cubic centimeters from the site of injection of the serum, is injected intradermally 0.1 cubic centimeters of polyvalent vaccine in the form of attenuated virus. In 10 days 0.1 cubic

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centimeters of vaccine alone is injected intradermally into the right-hand side of the neck in order to intensify the immunity. In the experiment M. Lignieres vaccinated 124 head of cattle by this method. As a result, one milk-cow developed foot-and-mouth disease two months after vaccination, 5 head of cattle 4 months afterward, 2 head 9½ months afterward, and 103 head remained healthy when situated for a considerable period in a locality contaminated with foot-and-mouth disease. According to M. Lignieres assertion, the vaccination did not in a single case bring about the occurrence and spread of foot-and-mouth disease on farms where inoculation was performed.

At a session of the Agricultural Academy in Paris in December 1936, Roussu, giving its due to the new scientific research of M. Lignieres in the field of active immunization against foot-and-mouth disease, nevertheless remarked that "it is necessary that Dr. Lignieres' experiments again be tested in practice".

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RATNER'S METHOD

In 1937, Ratner ("Experimental Data on Active Immunization in Foot-and-Mouth Disease". Sov. veterin., No 8, 1937, pp. 34-37.) published his results of his experiments with vaccination of cattle, with the conclusion that the "complex" vaccine which he had prepared (acetone vaccine plus convalescent serum) "in all instances gives a consistently positive result. The introduction of an additional factor -- convalescent serum -- into the method of preparing acetone vaccine has thoroughly justified itself. The complex vaccine imparts active and prolonged humoral immunity, which can aspire to one of the first places in solving the problem of prophylaxis against foot-and-mouth disease". These conclusions were made by the author on the basis of a small experiment on guinea pigs (only 15 guinea pigs in all were vaccinated). Later, Ratner performed experiments with active immunization of cattle under actual conditions. According to his data, "74 to 80 percent of the vaccinated animals acquire a sufficiently well-pronounced short-term immunity against foot-and-mouth disease. Immunity sets in less than 14 days after vaccination and disappears in the course of 30 days after it". These experiments, according to the author's declaration, "have basically confirmed the data obtained earlier on small laboratory animals". (Ratner. "Experiments in Active Immunization of Cattle". Sov. veterin., No 3, 1938, pp 17-19.)

Actually, the conclusions drawn by Ratner were in this case greatly exaggerated and were not derived from experiment. He

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completely failed, for example, to take into consideration animals with naturally acquired immunity, and in individual groups they amounted to 25.3 to 50 percent. For accounting and evaluation of clinical data he used an arbitary 4 point system -- absence of disease (—), weak development of disease (±), moderate development of disease (+), and strong development of disease (++) -- instead of the universally acknowledged, exclusively correct scientific system of accounting and evaluation of clinical data according to the nature of development of the foot-and-mouth disease process: (1) appearance of primary aphthae without subsequent generalization of infection with consideration of the time during which development of this process of foot-and-mouth disease takes place, and (2) the appearance of primary and secondary aphthae (the latter in consequence of generalization of the infection). Also admitted to the experiment were a whole series of methodological digressions which to a considerable degree render valueless the experiments performed by Ratner.

THE "DEPO" METHOD

For the purpose of causing a more prolonged immunizatory stimulus, Galea used the "depo" method. For this purpose he mixed the virus with vaseline and a small quantity of infusorial earth in order to cause a local inflammatory process. The results obtained varied.

In our laboratory Dubyanskiy and Khomenko performed experiments in the same direction on cattle, chloroform-vaccine in refined

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sunflower oil being used instead of virus. The vaccine was injected simultaneously together with the oil, mixing being accomplished right in the cylinder of the syringe before the injection itself.

Three small experiments on 22 head of cattle were performed. The results obtained were indeterminate.

Upon injection of vaccine and oil in increased quantities (no less than 10 cubic centimeters per head) the results were somewhat better. A group of cattle immunized by the usual method with chloroform-vaccine alone without grease were used as a control in performing the experiment. In this group of cattle the authors established the presence of a stable immunity capable of resisting artificial infection, while simultaneously infected unvaccinated cattle all developed foot-and-mouth disease. A trend of this nature in the solution of the problem of active immunization against foot-and-mouth disease deserves some attention, but is in need of more thorough experimentation.

OTHER METHODS OF VACCINATION

Toman, for purposes of active immunization against foot-and-mouth disease, prepared a formole-vaccine from the liver and spleen of animals killed during the period of generalization of the infection. Following inoculation there occurred only a slight inhibition of the course of development of the disease. Certain investigators have used as vaccine virulent blood treated in pre-

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liminary with formalin. Upon inoculation with this vaccine in doses of 50 to 75 cubic centimeters unsatisfactory results were obtained.

Vallee and Carre once used "hemo-vaccination" in the form of simultaneous inoculations. For this purpose they injected under the skin of animals convalescent blood in the amount of 1 cubic centimeter for each kilogram of live weight, and simultaneously or several days later injected, also under the skin, from 1 to 10 cubic centimeters of virulent blood taken from sick animals at the moment of generalization of the infection (hemo-vaccination). The inoculation, according to the authors' statements, imparted a stable and prolonged immunity to the animals without visible clinical development of the disease.

Moussu modified somewhat the method of Vallee and Carre in that he recommended injecting a convalescent blood not under the skin, but intravenously, in the amount of 20 cubic centimeters.

Rousseau performed intravenous injection of virulent blood, which had first been subjected to simultaneous defibrination and chilling, in the amount of 100 cubic centimeters. Terni and Lutrario used virulent blood intravenously, in the amount of 20 to 25 cubic centimeters injected three times at intervals of 10 days.

Cosco and Aguzzi performed immunization with erythrocytes which had first been washed off. These were taken from sick animals in the period of highest temperature increase. They

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injected from 10 to 35 cubic centimeters intravenously. After injection of the washed erythrocytes there developed, as a rule, general infection with temperature rise. Subcutaneous injection of even small doses of virus-containing erythrocytes almost always involves a typical form of development of foot-and-mouth disease.

In 1926, Belin suggested as a vaccine against foot-and-mouth disease "cow-pox -- foot-and-mouth disease complex" prepared by him from a mixture of the two viruses -- cow-pox and foot-and-mouth disease. According to his data, this vaccine produced good results in practice. However, other investigators could not confirm this, and Belin's method has not received practical application.

Spinola was one of the first to use intradermal injection of virus in the form of lymph from aphthae for the purpose of immunization in foot-and-mouth disease.

Bevan and Walker in Southern Rhodesia (1932) used, for purposes of immunization of cattle, pulverized virus on the membrane of the nasal cavity. They were forced to resort to such a method because active immunization by means of subcutaneous injection of virus, and also application of virus to the mucous membrane, did not succeed at all.

These failures with the infection of cattle through subcutaneous injection of virus, and also through application of it to the mucous membrane of the buccal cavity, they were inclined to explain by the exceptionally peculiar properties of the

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Rhodesian virus. Incidentally, Andrewes (England) holds that the method of intranasal inoculations used in Southern Rhodesia deserves serious attention. (Personal communication of Andrewes.)

It seems to us that it is unwise to overestimate the importance of this new method of inoculations, since all of these results could have been obtained in Southern Rhodesia due to the fact that foot-and-mouth disease is static there, and all these phenomena could be attributed exclusively to an acquired resistance on the part of local stock and to local conditions. In essence, the intranasal inoculations used in Southern Rhodesia, in our opinion, do not differ in principle from other methods of artificial infection.

Upon investigation in Pirbright (England) of strains of virus received from Southern Rhodesia, it turned out that when used to inoculate cattle they caused a typical clinical picture of foot-and-mouth disease, and the disease usually ran its course in severe form. Consequently, the reason for the mild form of foot-and-mouth disease must be sought in purely local conditions.

CONCLUSION

At the twelfth meeting of the International Epizootic Bureau in Paris (1938), questions connected with the development of methods of active immunization were reflected in a report and statements by Flückiger, who declared that "so far science has not found a completely effective method of active immunization against

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foot-and-mouth disease, but at present more than ever it is possible to hope that such a method will actually be found".

On the basis of Flükiger's report it was decided: "Scientific development of methods of active immunization against foot-and-mouth disease should continue further, both the direction of biological methods of attenuating the virus and in that of chemical methods".

From a more or less thorough study of data which have been published during the past 10 to 20 years it follows that the most hopeful appears to be vaccination against foot-and-mouth disease by means of using virus which has been inactivated but which has kept its antigenic properties. In principle there is not importance in the paths by which such inactivation may be achieved (biological, chemical, or physical), so long as it does not involve destruction of the antigenic structure of the virus.

At the same time, there must be no refusal to perform further experiments with the use of vaccine which has been killed, although solution of this problem seems extremely problematical to us. The possibility of forming immunity to foot-and-mouth disease without the appearance of visible specific afflictions, and also a clinically pronounced reaction on the part of the vaccinated animal's system must be considered proved at the present time.

On the basis of scientific research of Danish, German, and Soviet investigators the problem of active immunization against

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foot-and-mouth disease must be considered solved in principle. There is no need to discuss which of existing vaccines against foot-and-mouth disease is better or worse -- the future will show this. It is necessary to introduce into practice immediately those achievements which are available.

Every new vaccine can, in individual instances, produce unsatisfactory results and unpleasant complications during the first stages of its introduction into practice, but this should not delay familiarization with new methods of fighting foot-and-mouth disease.

Solution of the problem of vaccination against foot-and-mouth disease is one of the leading triumphs of veterinary science, and it will enter into history on a level with the classic discoveries in the field of biology and microbiology with which the nineteenth and beginning of the twentieth centuries were so rich.

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Editor, V. V. Chubinskiy

Technical Editor, N. A. Isakov Corrector, F. I. Vorob'yev

M-08423

Delivered to Press 11/17/1947 Quantity, 10,000

19.75 Printed Leaves and 3 Color Inserts V l p. l., 33,200 Symbols

Equivalent-Published Leaves, 19.66 Order No 427

Paper, 84X110 1/32

Fourth Printing Plant im. Evg. Sokolova of the Poligrafniga Trust of OGIZ under the Soviet of Ministers of the USSR Leningrad, Izmaylovskiy Prospekt, 29.

E N D

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