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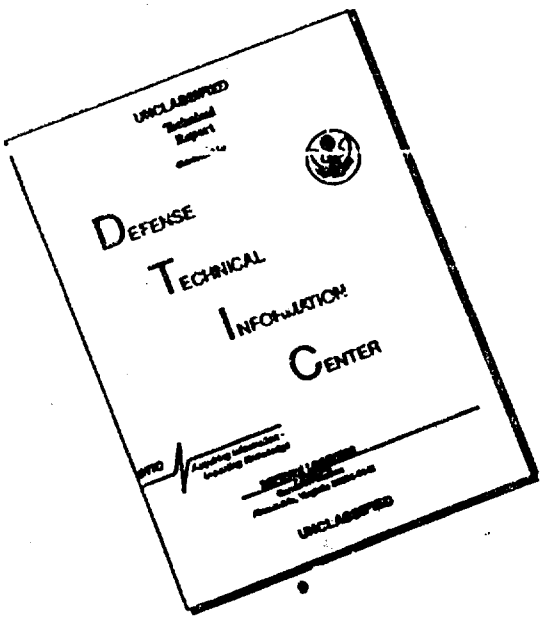

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TRANSLATION

The Coxsackie viruses which belong to the multitudinous group of enteroviruses are recently coming more and more into the center of attention of the researchers in various countries of the world.

At present, thirty immunologically different Coxsackie virus types are known. They are divided into two large groups: A (24 types) and B (6 types) according to classification (1) suggested by DALLDORF. The classification is based upon the nature of the pathological changes which these viruses produce at experimental inoculation into newborn white mice. Group A includes the viruses which provoke only scattered lesions in the skeletal muscles of newborn white mice. Group B unites the viruses whose inoculation into newborn white mice will cause changes not only in the muscles but also in the central nervous system as well as in other organs (brown fat, pancreas, heart, liver). Moreover, the muscular tissue lesions, caused by the B group viruses, have focal character in distinction from the lesions produced by the A group viruses.

The histopathology of experimental infection, caused by different representatives of the Coxsackie viruses, is not well known. In this respect, those Coxsackie viruses are particularly interesting which in human beings and in research animals cause diseases that cannot be clinically distinguished from poliomyelitis. As it is well known, the Coxsackie A-7 virus has such properties (2-11).

In 1957, DALLDORF (12) established on monkeys and white mice that the Coxsackie A-14 virus also has neurotropic properties. V.I. ZHEVANDROVA, M.K. VOROSHILOVA, I. K. LAVROVA (13) showed further on that the Coxsackie A-14 virus, just as the Coxsackie A-7 virus, produces a picture of experimental poliomyelitis in adult cotton rats. In monkeys and adult white mice, no clinically manifest sickness was noticed.

The histopathology of experimental infection caused by Coxsackie A-7 viruses is described in our previously published works (14-16).

(Page 62) In the present article we publish the results of morphological research made on monkeys, cotton rats, suckling cotton rats, white mice and their sucklings which were infected with the Coxsackie A-14 virus.

Title: Study of the histopathology of experimental infection with Coxsackie A-14 Viruses.

Author: M. . Frolova, et al

Source: Akademia nauk latviiskoi SSR , p 60-71

1962, Riga Vol. XVII

I

MATERIAL AND METHODS. We studied the central nervous system, the skeletal muscles, the internal organs, and the brown fat of two monkeys (Macaca rhesus), and 40 rodents (adult and newborn cotton rats, white mice and their sucklings) which were infected with the Coxsackie A-14 virus.

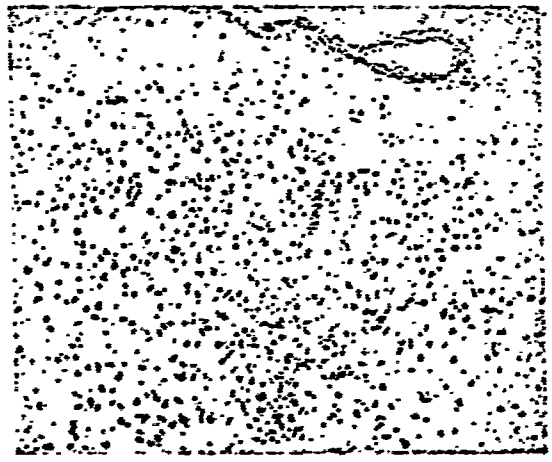

FIGURE 1: Inflammatory reaction in the pia mater, and areolar gliotic nodules in the cortex of the precentral gyrus of monkey No.622. Staining by Nissl's method. Microphoto 10 x 5.

The material was obtained from the Immunological Laboratory of our Institute where all the experimental infections were made, the animals were clinically observed, and this strain was virologically studied in detail. (V. I. ZHEVANDROVA and M. K. VOROSHILOVA).

Monkey No. 617 was inoculated with Coxsackie A-14 virus into the brain and the muscle, killed eight days after inoculation, although she showed no clinical symptoms of sickness. The other monkey (No. 622) was simultaneously inoculated with the virus into the brain and the spinal cord as well as intramuscularly. She was killed on the tenth day after inoculations, also without her having any signs of disease. The rodents were inoculated into the brain, intraperitoneally or subcutaneously with an emulsion made from the cadavers of suckling white mice. The emulsion contained the Coxsackie A-14 virus. The suckling cotton rats were killed 4 to 6 days after the inoculation, and they showed paresis and paralysis of the extremities. The [adult] cotton rats were killed 8-9 days after inoculation, and five of them had marked paralysis of the extremities, while three had no clinical symptoms of sickness. The adult white mice never became sick, and the newborn mice were killed 3-4 days after inoculation with symptoms of paresis or flaccid paralysis, or in a state of marked lassitude and reduced mobility. Normal, non-inoculated animals, their nervous system, internal organs and muscles served as control. The material was embedded in paraffine, stained with hematoxylin-eosin, and according to Nissl's method.

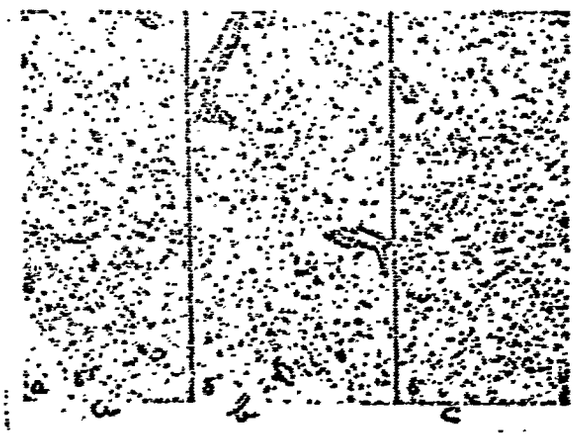

FIGURE 2. Diffuse inflammatory degenerative changes in the mesencephalon and the oblongata of Monkey No. 617: a...lesion of the nucleus ruber; b. changes in the reticular substance of the oblongata; c. the vestibular nucleus. Staining by the Nissl method. Microphoto 10 X 5.

RESULTS OF THE EXAMINATION. At microscopic examination of the central nervous system of monkeys, the neurotropic properties of the Coxsackie A-14 virus were distinctly shown. In both monkeys marked inflammatory degenerative changes were observed; in the brain and the spinal cord they were similar to the picture of experimental poliomyelitis, but more scattered in their localization. Death and outfall of neurons, small loose accumulations of cellular elements, and perivascular infiltrations around vessels were found not only in the motor cortex, as this takes place in case of poliomyelitis, but in the frontal, temporal, insular regions of the cortex also, moreover not only in the layer of the large pyramids but in all other layers also (Figure 1). Almost all the subcortical formations, the nuclei of the mesencephalon and pons, and of the oblongata and the cerebellum (the nucleus dentatus and the nuclei of the internal formation) were affected. (Figure 2). In the spinal cord, changes occurred in the cervical, thoracic and lumbar segments. The process was not limited to the area of the anterior horns, but it caught also the intermedullary zone and the posterior horns (Table 1).

In the foci of spinal cord lesions, neurons with severe necrotic changes, cells with different degrees of tigrolysis, and completely normal, unchanged neural cells could be seen. At the site of dying neurons the formation of neuronophagic nodules was observed. These nodules consisted of polyblasts, histioid and microglial elements, individual plasma cells (Monkey No. 622), and in a more acute stage (Monkey No. 617), large number of leukocytes with polymorph nuclei.

(Page 65) Parallel with the destruction of neurons and the formation of neuronophagic nodules there was diffuse infiltration of the brain tissue with cellular elements. A large number of perivascular sleeves was noted in Monkey No. 622 -- marked inflammatory reaction in the pia mater. By studying the localization of lesions along the spinal cord, we see that, at separate levels of the cord, different cell groups were attacked, moreover only a part of the neurons died in the foci of the lesion. A large portion of the neural cells was in a state of reversible changes, while a certain number of them was completely intact (Figure 3).

TABLE 1. MORPHOLOGICAL CHANGES IN THE CENTRAL NERVOUS SYSTEM OF MONKEYS INFECTED WITH THE COXSACKIE A-14 VIRUS

Site	Monkey No. 617	Monkey No. 622
Cerebral meninges	-	+
Frontal cortex	+	+
Motor cortex	+	++
Temporal cortex	++	++
Insular cortex	+	+
Caudate nucleus	+	+
Globus pallidus	+	-
Putamen	-	+
Thalamus opticus	+	+
Subthalamic area	+	+
Corpora quadrigemina	+	+
Substantia nigra	+/-	+/+
Nucleus ruber	+/-	++/++
Intrinsic nuclei of pons	+	+
Vestibular nucleus (VIII)	++/-	+++/++
Area reticulata	++	+++
Nucleus of VII pair of craniocerebral nerves	+/-	++/-
Nucleus of XII pair of " "	-/-	+/-
Nucleus of X pair of " "	-/-	-/-
Olivary nucleus	-/-	-/-
Goll and Burdach nuclei	-/+	+/-
Nucleus dentatus of cerebellum	-/++	-/++
Nucleus of internal formation of cerebellum	-/++	-/++
Cervical segment of spinal cord	+++/++	+/+
Thoracic segment of spinal cord	+/+	+/+
Lumbar segment of spinal cord	+++/++	++/++

NOTE: Here and [illegible] 2 the degree of the lesion's severity is marked [illegible]

FIG 2: Cervical segment of the spinal cord of Monkey No. 622. Foci of the lesion in the anterior and posterior horns. Staining by Nissl's method. Microphoto: Magnifying glass.

The neurotropic properties of the Coxsackie A-14 virus were noticed by DALLDORF on monkeys and white mice. We were the first to show the same properties of this virus on adult cotton rats also after both intracerebral and subcutaneous inoculation of the virus. Here, in the central nervous system we found changes not only in animals killed at the peak of clinical manifestations, i.e., when their extremities were paralyzed or paretic, but also in animals killed during the incubation period, without clinical symptoms of the disease. In adult cotton rats, changes were regularly found in the cortex, Ammon's horn, subcortical formations, mesencephalic and myelencephalic nuclei. In the spinal cord, only the cervical and lumbar divisions were more often affected; less frequently, the changes involved the whole length of the spinal cord, its anterior and posterior horns. Here, degeneratively changed neurons, death and outfall of a large number of motor neurons, marked diffusion of proliferative glial reaction, marked vascular mesenchymal reaction could be observed (Figure 4).

In the central nervous system of suckling cotton rats and suckling white mice which were inoculated with Coxsackie A-14 virus, we had not found any specific changes.

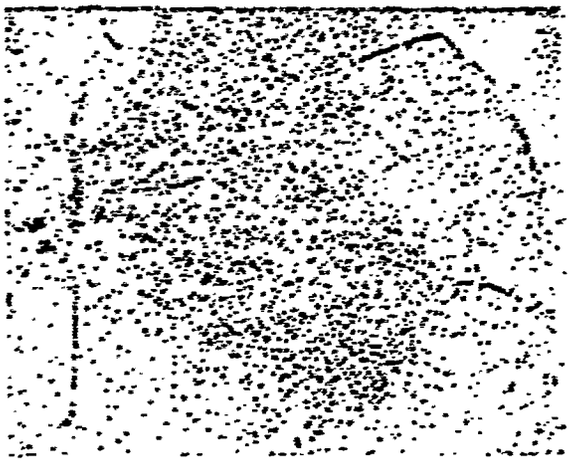

FIGURE 4: Death and outfall of neurons, diffuse inflammatory reaction in the spinal cord of an adult cotton rat, infected with Coxsackie A-14 virus. Staining by Nissl's method. Microphoto 10 x 5.

As we have previously said, the white mice did not get sick when inoculated with the Coxsackie A-14 virus. However, at microscopic examination of the central nervous system of white mice killed 8-9 days after their inoculation with the virus, eight out of 10 animals showed distinct lesions in the brain and the spinal cord. These lesions were similar in character to the process seen in adult cotton rats, but of less intensity. The lesions occurred after inoculations by either the intracerebral or the subcutaneous methods.

In the skeletal muscles of suckling white mice and cotton rats, the histological examination showed the widely scattered necrotic changes characteristic for all representatives of the Coxsackie A virus group. The affected muscular fibers were deprived of their transverse striation. They were swollen, and they broke into fragments of different sizes of intensively eosinophil hyaline lumps. At some places, the fragments underwent a fine-granular decay. At these sectors, nodular accumulations of polyblasts were found, together with proliferating nuclei of muscular fibers and individual leukocytes (Figure 5).

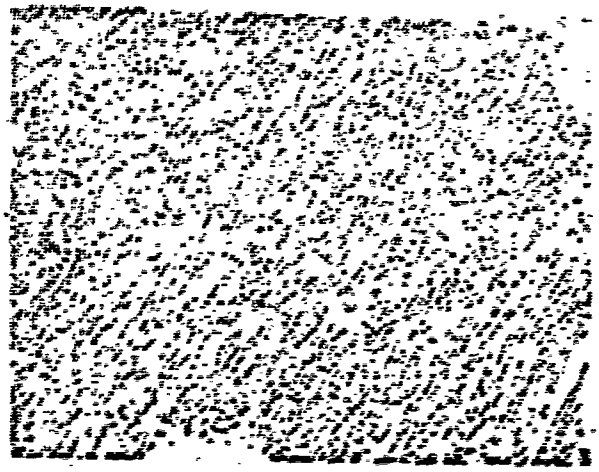

FIGURE 5: Skeletal muscle of a suckling white mouse. Zenker necrosis of the muscular fibers. Staining with hematoxylin-eosin. Magnification 10 x 10.

In the skeletal muscles, necrotic changes occurred in both adult white mice (in 8 out of 10) and adult cotton rats (in 3 out of 3). As a difference from the muscular changes found in suckling white mice and cotton rats, the muscular changes in adult animals had a definitely focal character. In all suckling cotton rats, beside the widely scattered lesions in the skeletal muscles, changes occurred also in the myocardium where they appeared as focal necrosis of muscle fibers (Figure 6). The muscles fibers in the necrotic sectors were swollen, strongly eosinophil, and they broke down into hyalin fragments of different sizes. Sometimes in these sectors, moderate infiltration of leukocytes and polyblasts could be seen (Figure 7). In some cases the hyalin fragments underwent fine granular decay, and the myocardial foci of lesions were represented by fields composed of collapsed stroma and spindle cells with transparent vesiculiform and elongated nuclei among which a few lymphoid elements and individual disintegrating leukocytes were met with. Fibrous scarring was

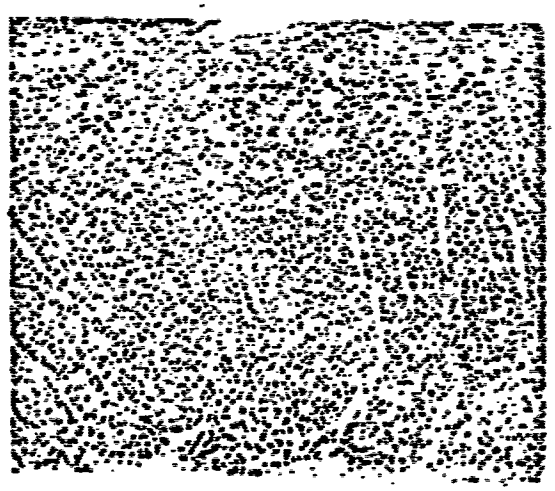

FIGURE 6: Wall of the left heart ventricle of a suckling cotton rat. Necrotic Focus of muscle fibers (Overall view). Staining with hematoxylineosin. Magnification: 10 x 10.

FIGURE 7: Necrotic focus of the heart muscle of a suckling cotton rat. Fragmentation, lumpy and fine-granular disintegration of the muscular fibers. Staining with hematoxylin-eosin. Magnification: 20 x 10.

not seen at the site of death of the muscular fibers, not even in a single instance. Necrotic foci of the myocardium occurred in both ventricular and atrial walls, and in the interventricular septum. Lesion of the pericardium and endocardium was not observed. In other internal organs, no changes were found. In the internal organs of all other examined animal species no specific changes were found.

EVALUATION OF THE RESULTS. These histological examinations showed that in addition to those widely scattered lesions in the skeletal muscle in suckling white mice which are characteristic for all Coxsackie A group viruses, the studied Coxsackie A-14 virus strain also produced polio-myelitis-like changes in the central nervous systems of monkeys, adult cotton rats and white mice. Our data as to monkeys and white mice are in agreement with the data of DALLDORF (DALLDORF did not study the Coxsackie A-14 virus on cotton rats) (12). The ability to produce changes in the central nervous system of monkeys and cotton rats brings the Coxsackie A-14 and the Coxsackie A-7 viruses closer together. In connection with this, we consider it appropriate if the evaluation of results obtained at the histological examination of animals infected with the Coxsackie A-14 virus is compared with those results that we got earlier, while studying the histopathology of experimental infection produced with the Coxsackie A-7 virus (14-16).

TABLE 2. HISTOLOGICAL FINDINGS IN ANIMALS INFECTED WITH THE COXSACKIE A-7 AND A-14 VIRUSES

Experimental animals	Centr. nerv. syst.		Skelet. muscles		Internal organs	
	A-14	A-7	A-14	A-7	A-14	A-7
Monkeys	++	+++	-	-	-	-
Adult cotton rats	++	+++	+	-	-	-
Adult white mice	+	-	+	-	-	-
Suckling cotton rats	-	++	++	++	+	-
Suckling white mice	-	+-	+++	+++	-	-

The comparison makes it obvious that the studied Coxsackie A-14 virus, although it has properties which bring this virus closer to the Coxsackie A-7 virus, also possesses a number of differences. These differences are that the Coxsackie A-14 virus causes changes in the transversely striated muscles of adult white mice, more infrequently of cotton rats, while in suckling cotton rats it regularly affects the myocardium. Moreover, the Coxsackie A-14 virus attacks the central nervous system of adult white mice, by causing in these animals poliomyelitis-like changes, but it does not lead to lesions in the central nervous system of newborn white mice and suckling cotton rats.

The obtained results show that, after comparison with the Coxsackie A-7 virus, the A-14 virus has less expressed neurotropicity with more emphasized myotropicity. The weakness of neurotropic properties in the A-14 virus is manifested firstly so that it does not produce changes in the central nervous system of suckling white mice and cotton rats, and secondly so that, in monkeys and adult white mice, lesions of the central nervous system are not accompanied by clinical symptoms of an infection of these animals. The absence of neurological symptoms in monkeys and adult white mice infected with Coxsackie A-14 virus is connected with peculiar features of the pathological process in the central nervous system of these animals. In monkeys a mosaic pattern is observed in the wide scattering of pathological foci: at different levels different cell groups are affected, while in the same foci there are always cells with slight dystrophic changes, and neurons which are entirely unchanged. All this, together with the compensating facilities of the nervous system, explains also the absence of neurological symptoms in an exceedingly diffuse pathological process. The changes are weakly expressed in the central nervous system of white mice.

The easier expressibility of the myotropic properties of the Coxsackie A-14 virus comes to light in lesions of the transversely striated muscles in adult white mice and cotton rats as well as in lesions of the myocardium in suckling cotton rats.

Thus, as the Coxsackie A-7 virus, the Coxsackie A-14 virus has also both myotropic and neurotropic properties and this fact distinguishes these viruses from all other representatives of the Coxsackie A-group viruses, bringing them closer to the virus of poliomyelitis. It may be thought that the enteroviruses which possess neurotropic and myotropic properties are transient forms between the poliomyelitis virus and the Coxsackie group of viruses, and they are best separated in a special group. For the Coxsackie A-7 virus, its etiological role was unquestionably

proved in paralytic diseases of man which cannot be clinically distinguished from poliomyelitis (4-7). As to the Coxsackie A-14 virus, even though such evidences are missing at the present time, such a possibility cannot be entirely ruled out. This problem requires a further, consciously aimed study.

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