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WITH LIVE ATTENUATED VACCINE

-USSR-

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EXPERIENCE IN VACCINATING AGAINST POLIOMYELITIS WITH
LIVE ATTENUATED VACCINE

-USSR-

Following is the translation of an article by A.S. Pentsik, F. M. Lisitsa and N. P. Pakalsh (Riga) in Klinicheskaya Meditsina, Vol. 38, No. 9, Moscow, 1960, pages 48-53/

Gradually spreading from separate, ever expanding endemic foci, the incidence of acute poliomyelitis has by the middle of the 20th century attained considerable proportions. This indicated the inefficiency of the curative and prophylactic means which mankind possessed at that time for combating poliomyelitis. The attempts made before the Second World War to evolve an effective vaccination against poliomyelitis proved unsuccessful. The situation changed substantially for the better after the possibility was established of multiplying the poliomyelitis virus outside of the nervous system -- in cultures of monkey and human tissues in vitro (tonsils, kidneys, etc.). The virus causes a characteristic degeneration of the cells in the tissue culture. This cytopathogenic action is repressed when the specific neutralizing serum is added. This enables one to determine the polio virus in vitro, to titrate the antibodies and obtain antigens for serological reactions, virus for vaccine, etc.

The research aimed at solving the problem of active immunization against poliomyelitis was from the very beginning carried on in two main directions: 1) immunization with killed poliomyelitis virus and 2) immunization with live diluted virus. At the beginning of the 1950's preference was given to immunization with killed virus (Salk and others), which gained wide distribution in various countries (USA, Canada, France, FGR, Finland, Sweden, England, Italy and others). A number of methods were proposed for preparing this vaccine. Millions of persons were vaccinated with killed poliomyelitis virus in 1954-1957. In a considerable part of those inoculated a growth was recorded in the titer of antibodies to poliomyelitis in the blood serum, chiefly

after triple inoculation. In the Latvian SSR anti-polio-myelitis inoculations were also made with Salk Vaccine in 1956-1957 on large contingents of the child population.

With the application of this vaccine the incidence of paralytic poliomyelitis dropped perceptibly in various countries. Mortality from poliomyelitis became much lower than at any time in the 20th century (about 4%). However, experts from various countries meeting at a special conference in Copenhagen (14-19 April, 1958) were unable to solve definitively the question of whether the diminution in the incidence of poliomyelitis is a consequence of the extensive vaccination with killed virus or whether it is only an expression of a certain periodicity in poliomyelitis epidemics.

In 1958 a growth was observed in the incidence of the paralytic form of poliomyelitis, principally among non-vaccinated or incompletely vaccinated groups of the population, but also partially among vaccinated persons (for example, in Detroit). Control research has shown that even people who have been fully vaccinated with the killed virus remain un-immunized and consequently receptive to poliomyelitis in 20-30% of the cases, perhaps even a larger percentage. Hence, in 1958 many specialists were already far from the enthusiasm which reigned in the spring of 1955 with respect to the victory over polio. Obviously, further research was necessary for the purpose of obtaining a more effective vaccine capable of causing the development of a high and stable immunity to polio in vaccinated persons.

By this time the study of live vaccine had given encouraging results in the sense that immunity was obtained in those vaccinated (Koprowski, 1956; Sabin, 1959; Dane, 1958; Horstmann, 1959). However, the question of the degree of safety of this mass vaccination for surrounding persons remained unclear, since the virus of the vaccines introduced through the mouth is secreted with the feces. Nor has it been established to what degree this virus is dangerous to the vaccinated person himself. Many other questions connected with the employment of dilute live polio virus for vaccination have not been solved. These questions concern the immunogenic potency of the live vaccine, its influences on the flora of the intestines, the influences of anti-polio vaccination on the receptivity of the inoculated to other infections, above all to intestinal viruses, etc.

In the spring of 1959 the epidemiological service of the Ministry of Public Health of the Latvian SSR at

the initiative and under the direction of Prof. A. A. Smorodintsev, undertook vaccination with live dilute anti-polio vaccine introduced per os. During February to May 1959, large contingents of the population of the Republic (of different age groups), totalling over 400,000, were vaccinated twice. The vaccinating was done with three types of dilute polio virus: in the first vaccination type I of the virus was introduced; in the second (a month after the first), types II and III together.

Final appraisal of the effectiveness of this vaccination can probably not be given for some years. However, some results can already be dealt with now.

First of all it is to be noted that polio incidence in the Latvian SSR in 1959 was the lowest during all the postwar years. All of the stationary dispensaries of the Republic to which sufferers from polio or polio-like ailments are usually sent received from various parts of the Latvian SSR between May and December 1959, 44 patients suspected of having polio. There were 19 males and 25 females. Thirteen of the patients were up to five years of age; nine from 6 to 10; ten from 11 to 15; three from 16 to 20; and nine more than 20 years of age.

Twenty-seven of the 44 had not been inoculated. Among the non-inoculated, 24 had contracted a paralytic form of polio, including one bulbar and one bulbo-spinal form, two polio-like ailments (presumably caused by "echo" viruses) and one case of serious meningitis of unclear etiology. The remaining 17 had received inoculation against polio, and the analysis of this group presents the greatest interest; the 17 inoculated persons were distributed as follows: three inoculated with killed Salk vaccine, 12 with live vaccine per os, two with killed vaccine in 1957-1958 and then with live vaccine in 1959.

The three children inoculated only with killed vaccine had contracted the disease: two the paralytic form of polio (one girl died and the autopsy confirmed the diagnosis of polio), while the third girl had suffered an unclear infection with fever temperature, with noticeable symptoms of irritation of the cerebral membranes, a smoothing of the left nasolabial fold and Babinski's symptom and the left; the outcome was favorable. Our attention, of course, was attracted chiefly to the patients who had received live anti-polio vaccine. In four out of 14 patients (12 inoculated only with live vaccine, two with Salk vaccine and live vaccine) the ailment was clinically similar to polio, but polio was not confirmed by the laboratory; polio-like ailments and serious meningitis of unclear etiology had developed in seven; there

were acute gastro-intestinal disorders in three.

Let us dwell in more detail on each of these three groups of patients.

1. Patients with poliomyelitis not confirmed in the laboratory.

Male patient F., age 2 years, 6 months. In September 1958, was inoculated twice with Salk vaccine; in April and May, 1959, received live anti-polio vaccine; on 27-28 August 1959, an acute intestinal infection with fever temperature set in; there was vomiting and diarrhea; on 15 September, at normal temperature, pains and weakness in the legs appeared, Upon hospitalization in the children's ward, rigidity of the cervical muscles and Kernig's symptom were furthermore noted. Analysis of the spinal fluid: albumin 0.39 per mil, cytose 17/3, lymphocytes. Dynamic laboratory investigation revealed only a certain increase in the titer of antibodies to polio virus of type I from 1:16 to 1:64. Complete recovery.

A diagnosis of polio cannot be ruled out in this patient. However, the immunity reaction was very feebly pronounced.

Male patient S., age 2. In September-October 1958, was inoculated with Salk vaccine, and on 10 April 1959, received per os live vaccine of type I. Fell ill on 18 April: temperature rose suddenly to 40°, then kept at fever level for three days; swelling of face and legs also occurred. From 22 April on, temperature normal, swellings subsided. On 11 May received second inoculation with live vaccine, on 12 May general weakness was noted. On 17 May limp paresis of the right leg developed. On 18 May temperature rose to 40°, and on 21 May paresis also appeared in left leg. Analysis of spinal fluid: albumin 0.06 per mil, cytose 0/3. Polio virus not detected in feces. In the blood, a high titer of antibodies was discovered to all three types of polio virus in the very first examination.

This observation is especially difficult to analyze. The ailment which set in after the first introduction of live vaccine in April 1959, was evidently allergic. After the second introduction of live vaccine there was acute illness with high temperature and asymmetric atonic paralyzes of the legs, without change in the spinal fluid and with a high titer of antibodies to polio. What was this: a peculiar allergic reaction or did the anti-polio inoculations activate another virus (or viruses) and lower the resistance of the organism to one of the polio-like ailments? The possibility of interference between the polio virus and certain intestinal viruses is being studied

at the present time. The clinical analysis of the outbreak of cases that occurred during the period of vaccination with live vaccine in 1959 in one of the rayons of the Latvian SSR (Autš) has enabled one of us (F. M. Lisitsa) to express a supposition about the connection of this outbreak with the possible interference of viruses: the polio virus and other viruses, possibly of the intestinal group. Our clinical observations relating to later occasional cases encountered in various rayons of the republic permit one to confirm this sort of possibility.

Male patient K., 17 years old, entered the rayon hospital on 8 May 1959, because of weakness in the right leg. On 23 April 1959, he had received per os type I live vaccine. Almost two weeks later (5 May) pains appeared in the muscles of the legs, headache, temperature 37.4°; the next day temperature reached 38°. Upon admission to hospital, atonic paresis of the right leg was discovered; tendon reflexes in this leg were not detected. Polio virus not found in feces. Blood and spinal fluid not investigated. Rapid and complete recovery.

In this case it was clinically possible to suspect polio, but the absence of laboratory data does not permit this diagnosis to be considered fully reliable.

Female patient D., age 2 years, 6 months. In spring of 1959 received double inoculation with live anti-polio vaccine. Fell ill on 12 November 1959, when it became hard for her to stand on right leg; body temperature normal. Upon entry into hospital (15 Nov.) atonic paresis of right leg was noted; tendon reflexes $d < s$. Blood analysis (15 Nov.): leucocytes 10,400; ROE 13 mm per hour. Spinal fluid (16 Nov.): albumin 0.079 per mil, cytose 3/3, sugar 72 mg%. Complete recovery in two weeks.

Clinically we regarded this disease as a light form of paralytic polio. The possibility is not ruled out that the favorable course of the disease in the last two cases was due to the anti-polio inoculations. The absence of dynamic virological investigations renders a definite conclusion difficult.

II. Group of polio-like syndromes

Female patient V., aged 14. Inoculated with live anti-polio vaccine (type I in April, types II and III in May 1959). Fell ill on 18 May 1959, six days after second inoculation and 5 weeks after first: pains appeared in throat, paresis in both legs, more sharply pronounced in the left; pains in the nerve trunks of the legs and their limbs when walking, positive Kernig and Laseg symptoms, reduction of the sensitivity of arms and legs as in the

polyneuritic type, absence of tendon reflexes in arms and legs, general asthenia. Spinal fluid (26 May): albumin 4.62 per mil, cytose 21/3, Pandy reaction + + +. Blood analysis (26 May): leucocytes 12,800; 28 May: Hb 74%, l. 8950, e. 3%, p. 2%, s. 61%, lymph. 31%, mon. 3%; ROE 12 mm per hour. Complete recovery in a few months.

In this case a clinical picture of polyradiculoneuritis was observed with albumin-cell dissociation in the spinal fluid (Guillain-Barre type), of unclear etiology. The disease differed from poliomyelitis in the polyneuritic type of the disturbances of the sensitivity, in the long delay in the root-neuritic pain syndrome, in the albumin-cell dissociation of the spinal fluid and in the comparatively rapid and complete convalescence.

Male patient K., age 16. Received per os live anti-polio vaccine on 9 April and 21 May 1959. Fell ill 16 June 1959: pains and weakness appeared in right leg. There had been an analogous ailment half a year before. Upon inspection in the hospital of infectious diseases there were noted a temperature rise to 37.7°, weakness of right leg, absence of knee and Achilles tendon reflex in right, hypotrophy of the quadriceps of the right leg, painfulness in right sciatic nerve when walking, disturbance of sensitivity in zone of nervus saphenus dext. Spinal fluid: albumin 0.99 per mil, cytose 16/3 (lymphocytes). In blood analysis, ROE 40 mm per hour; hemogramm within normal limits. Unconvincing flow of titer of antibodies to poliomyelitis noted in blood:

	type I	type II	type III
Serum I	1:16	1:64	1:64
Serum II	1:64	1:64	1:64

This ailment, which at first sight presents a polio-like clinical picture, was assessed by us as meningo-radicularitis of the lumbar section. The initial contraction occurred half a year before inoculation, but then, some time after inoculation, a reaction occurred in the zone of the earlier affected limbs and the right sciatic nerve.

Male patient M., age 11. In February-March 1959, received live anti-polio vaccine. Fell ill on 26 July 1959: pains appeared in right half of face. Hospitalized on 29 July, neuritis of the right facial nerve being noted. Extremities normal. Spinal fluid: cytose 18/3; albumin not determined. Course very torpid. Discharged without complete restoration of mimic innervation on 3 Sept.

The lack of adequate laboratory data in this case makes a definitive diagnosis difficult. To judge from the clinical results, one may think of a non-specific affection of the facial nerve itself. Special attention to this patient was aroused solely by the fact that he had at one time received live anti-polio vaccine.

Female patient R., age 2. Inoculated with live anti-polio vaccine in April of 1959. Fell ill on 3 November 1959; general sluggishness appeared, she was unable to walk or stand because of pain in right leg and back; hyperesthesia was observed; temperature rose to 37.2°. Hospitalized in children's clinical hospital on 4 Nov.

On entry, does not hold head up; pains and weakness in right leg, knee reflexes decreased, pains in back, Laseg symptom in right side and Neri symptom; general hyperesthesia. In blood analysis; ROE 38 mm per hour, leucocytes 6,900. Spinal fluid: albumin 0.083 per mil, cytochrome 2/3, sugar 58 mg%; on 9 Nov. leucocytosis reached 14,200; Spinal fluid: albumin 0.091 per mil, cytochrome 4/3, sugar 50mg%. Temperature remained subfebrile for a long time in stationary dispensary. In blood analysis of 19 Nov., 10,400 leucocytes. Rapid and complete recovery.

In this case a diagnosis of acute polyradiculoneuritis of the lumbo-sacral section is the most probable.

Female patient N., age 11. In April-May 1959, received double inoculation with live anti-polio vaccine. Fell ill on 8 September 1959; sent to children's clinical hospital on 10 September.

On entry, complained of headache. Rigidity of muscles in nape of neck and Kernig and Brudzinskiy symptoms noted. Next day, disturbance of innervation of face and tongue on left side and left-side hemiparesis noted. In night of 11 September attack of convulsions developed, with loss of consciousness. Temperature subfebrile, with rare rises above 38°. In blood analysis: ROE 4 mm per hour, leucocytes 12,500. Spinal fluid: albumin 0.062 per mil (10 Sept.), 0.124 per mil (11 Sept.), cytochrome 2/3. In blood analysis of 15 September: leucocytes 8,200. Rapid and complete recovery.

In this case the clinical diagnosis was meningo-encephaloradiculoneuritis, the etiology of which remained unascertained. The relationship of this infection to poliomyelitis is doubtful; if it were not for this patient's case history of inoculation with live vaccine, this ailment would not have caused any hesitation. An analogous ailment was observed in still another female patient.

In one girl of this group, as mentioned earlier, serious meningitis developed, which likewise would not have attracted attention if it had not occurred in the period of vaccination against polio.

Female patient P., age 7. Received live anti-polio vaccine on 14 April and 18 May 1959. Fell ill on 2 June 1959, when headache, vomiting and subfebrile temperature appeared. Entered rayon hospital 6 June. On entry, headache, a single fit of vomiting, slight meningeal syndrome, febrile temperature noted. Blood analysis: Hb 72%, 1,8860, eos. 1%, p. 4%, s. 80%, lymph. 11%, mon. 4%. Virological examination of feces for polio gave negative results. Ailment took a wholly favorable course.

III. Patients suffering from acute gastro-intestinal disorders (side phenomena of vaccination)

Female patient S., age 7, entered children's clinical hospital 21 April 1959; on 18 April 1959, received per os live anti-polio vaccine. Next day fell acutely ill: frequent vomiting, diarrhea, fits of pain in stomach. On entry into hospital there was vomiting, painfulness of stomach was noted upon palpation. No symptoms of irritation of cerebral membranes. Temperature subfebrile for three days. Spinal fluid: albumin 0.099 per mil, cytose 2/3. Acetone detected in urine. Rapid recovery in a few days.

We observed three patients with such disturbance. Not excluded is the possibility of more frequent, more slowly proceeding gastro-entero-colitic reactions that do not require hospitalization and are, therefore, not taken into account.

In this connection it is appropriate to recall that in anti-polio vaccination with killed virus apparently allergic side phenomena of various degrees of gravity have repeatedly been described: reddening of the skin and pains at the place of injection, fever, vomiting, nettle rash, sometimes convulsions. In the USA, two cases of encephalitis, five cases of myelitis and one case of sudden death, which could not be explained even after autopsy, have also been described after inoculations with Salk 2 (Nathanson, 1957). Uehlinger in Switzerland (1957) has reported still another case of sudden death of Salk inoculations.

Liebe and Woeckel (1958) of the FGR have described a fatal case of ascending Landri paralysis after Salk inoculation. Such grave complications have thus far not been noted in vaccination with live polio virus.

The above data show above all that vaccination with live polio virus does not itself produce grave consequences and that it is safe. The incidence of polio among those inoculated is insignificant, even if one takes doubtful cases into account. It does not exceed one case in 100,000 inoculations. Besides, among the persons who have received live vaccine polio-like ailments, most often of un-ascertained etiology, are likewise few in number (two cases out of 100,000 inoculations). The absolute figures here are insignificant, but the relative preponderance of polio-like forms requires further careful observation of the inoculated groups for the purpose of clarifying the question of the significance of anti-polio inoculations for the activity of other viruses. In particular, it should be mentioned that in one of the rayons of the Latvian SSR, where vaccination with live dilute polio virus was extensively carried out in the fall of 1959, there has been an outbreak of lymphocytic choriomeningitis, proved in the laboratory.

Conclusions

1. The total incidence of poliomyelitis in the Latvian SSR dropped sharply in 1959.
2. Among the persons vaccinated with dilute live polio virus, the incidence of paralytic forms dropped to insignificant figures in the next epidemiologic season. The course of these ailments was, as a rule, favorable.
3. Polio-like ailments in the group of persons vaccinated with live vaccine were encountered relatively more often than paralytic polio. This requires further observation and adequate explanation.
4. Now and then, dyspeptic side phenomena are encountered in vaccination with live dilute polio virus per os. They obviously demand consideration of the individual reactivity of the persons to be inoculated and detailed virological investigations.

LITERATURE

[All entries are in Latin letters].

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