and that breast-feeding should not be allowed. The choice of the anticoagulant drug is also to be considered. In a recent case of cerebral embolism occurring two weeks prior to term we used only heparin; the patient fully recovered, and heparin produced no ill effects in the mother or baby. Obviously, much wider clinical experience is needed in this particular field.

The many variable factors, including mitral-valve surgery in several patients before or during pregnancy, made an assessment of the remote effects of pregnancy on the course of the heart disease rather difficult. Furthermore, Rowe *et al.* (1960) suggested that medically treated patients with mitral stenosis probably live longer now than they did ten or twenty years ago. Nevertheless, consideration of data reported in the literature (Olesen, 1955; Wood, 1956; Rowe *et al.*, 1960) and our own observations relating to the natural history of rheumatic heart disease have led us to believe that pregnancy, if appropriately managed and survived, does not accelerate the course of rheumatic heart disease, save perhaps in exceptional cases. This is also the view of several other workers (Miller and Metcalfe, 1956; Burwell, 1958; Gorenberg and Chesley, 1958).

Summary

The course of 60 pregnancies complicated by rheumatic heart disease and paroxysmal or established atrial fibrillation is analysed, and some of the features are compared with those observed in 700 pregnancies with rheumatic heart disease in which sinus rhythm had been maintained throughout pregnancy and the puerperium.

The incidence of heart failure and embolic episodes was higher in the atrial fibrillation group, resulting in a higher maternal mortality rate and foetal loss. However, improved methods in the care of the pregnant patient with functionally severe heart disease have considerably reduced these risks.

The belief is expressed that if atrial fibrillation appears during pregnancy or in the puerperium an attempt should be made to restore sinus rhythm. Anticoagulant prophylaxis, if judged advisable, is also feasible during pregnancy.

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VIRUS EXCRETION AFTER MASS VACCINATION WITH ATTENUATED POLIOVIRUSES IN HUNGARY

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Hungary experienced her most extensive poliomyelitis epidemics in the years 1957 and 1959 (Rudnai, 1958, 1960). Both were caused by the type 1 poliovirus (Molnár, 1958; Földes *et al.*, 1959; Mécs *et al.*, 1961; Dömök and Molnár, 1961). The 1959 epidemic provided evidence that poliomyelitis epidemics might be moderated but not prevented by the wide-scale use of the Salk vaccine (Bakács, 1960; Rudnai, 1961). The excellent results of the oral vaccination with the Sabin strains in the U.S.S.R. (Chumakov *et al.*, 1959) induced Hungary to organize nation-wide vaccination with the same vaccine. During November 3–5, 1959, children from 3 months to 15 years of age were eligible in one county (Győr-Sopron county) for feeding trivalent vaccine containing 100,000 CPD50 of each type per dose. The same children were revaccinated with the same dose of trivalent vaccine during December 17–19, 1959. The average acceptance rate was 96%. Subsequently the children of the same age-groups were eligible for vaccination in the whole country, except for Győr-Sopron county. In this case the single types were fed separately in the following periods: type 1, December 14–19, 1959; type 3, January 21–27, 1960; type 2, February 23–27, 1960. The average acceptance rate was 92.4% (Kátay, 1961).

Virus excretion was studied in connexion with both campaigns. We wished to obtain data (1) on pre-vaccination excretion of enteroviruses; (2) on post-vaccination excretion by age of the Sabin strains; (3) on the relative effectiveness of simultaneous feeding; (4) on the effectiveness of refeeding the trivalent vaccine; and (5) on the interactions between wild enteroviruses and the vaccine strains, and among the vaccine strains. The reproductive capacity at 40° C. (Sabin, 1961) of the strains excreted by healthy subjects on the days preceding vaccination and of those reisolated from healthy vaccinees was also studied.

Organization of the Studies

(a) *Győr-Sopron County*.—The county's public health and epidemiological station was requested to collect faecal samples from a total of 160 children, selecting 20 children from each of the three towns and five districts of the county. The children were to fall equally in the five age-groups as follows: 3 to 23 months, 2 and 3 years, 4 and 5 years, 6 to 9 years, and 10 to 15 years, and only one child was to be chosen from the same child community (nursery, kindergarten). The schedule of sampling was as follows. Three samples were to be taken from every selected child in the period from one to five days before each feeding; post-vaccination samples were to be taken at 3, 5, 12, 15, 22, and 24

days (18 samples per child altogether). The plan was executed with slight changes. Instead of 32 per age-group, 34, 31, 31, 26, and 28 children were selected from the five age-groups listed above. All the 18 samples had arrived in this laboratory from 30, 23, 30, 33, and 25 children, respectively.

(b) *The Nation-wide Campaign.*—Of the 18 counties and five towns included in the campaign, nine counties (Baranya, Bács-Kiskun, Csongrád, Fejér, Pest, Szabolcs, Tolna, Vas, and Zala) and the town of Budapest were involved in the laboratory study. From each of the 10 areas 30 children under 4 years of age were planned to take part. Only one of them was to belong to the same nursery or kindergarten. Two faecal samples were to be taken in the period from one to five days before, and one sample at both three and seven days after, feeding each vaccine strain. Samples were received from 290 children instead of 300 as planned. All the 12 specimens arrived from 226 individuals. Their ages were 3 to 6 months in 29; 7 to 12 months in 76; 13 to 23 months in 84; and 2 to 3 years in 37.

Collection and Preparation of Faecal Specimens.—The faecal specimens were sent in in the usual containers, by ordinary mail, each with a specimen history on a form designed for this special purpose. Of the specimens sent in from Győr-Sopron county, the pre-vaccination ones, and of the post-vaccination samples the 3-day and 5-day samples, the 12-day and 15-day samples, and the 22-day and 24-day samples were mixed before being examined. Of the samples collected during the nation-wide campaign, the two prevaccination specimens as well as the two post-vaccination specimens were mixed. The mixed specimens were ground in a mortar each, and suspended in 10 volumes of Hanks's solution. The suspensions were centrifuged at 16,000 r.p.m. for 20 minutes, and after antibiotics had been added the supernatants were stored at -30°C . until used. Every sample was tested in monkey-kidney-cell cultures; those from Győr-Sopron county were also tested in suckling mice. The methods have been published elsewhere (Dömök *et al.*, 1960).

Typing of the Isolates.—The strains which had been isolated in monkey-kidney cultures were tested with the following typing sera: poliovirus 1, 2, and 3; E.C.H.O. 1-15, 17, 19, and 20; Cocksackie A 9, B 1-5. Those isolated in baby mice were tested with the Cocksackie A sera types 1-18. The polio and E.C.H.O. sera were prepared in rabbits, the Cocksackie sera in mice (Dömök *et al.*, 1960).

Reproductive capacity at 40°C . (rct/40) (Sabin, 1961) of poliovirus strains was determined in rhesus-monkey-kidney-cell cultures. The first or second tissue-culture-passage materials were used. Parallel titrations were made at $36\pm 0.2^{\circ}\text{C}$. and $40\pm 0.2^{\circ}\text{C}$. Three tubes were inoculated with each dilution. The results were read after seven days' incubation. The log difference in titre at 36°C . and 40°C . was calculated and divided by the similar log value for reference strain. A strain was regarded at rct/40⁻, rct/40[±], and rct/40⁺ if the quotient was >0.75 , between 0.3 and 0.75, and <0.3 , respectively (Benyesh-Melnick and Melnick, 1959). As rct/40⁻ reference strains the Sabin vaccine strains (L Sc, 2 ab; P 712, Ch, 2 ab; Leon 12 a,b) were used (Sabin, 1957).

Results of Studies of Trivalent Vaccine in Győr-Sopron County

The isolation rates are illustrated in Fig. 1. Before the primary feeding of the trivalent vaccine a large proportion of the children had excreted virus—52 of the 160 individuals tested. Polio, E.C.H.O., and Cocksackie viruses were isolated in 15.6, 10.0, and 6.9% respectively. In the youngest age-groups 50% of the children had excreted enterovirus. The type distribution by age is presented in Table I.

In the first week after the primary immunization with the trivalent vaccine 76% of the children tested proved to be virus excretors. This percentage decreased to 62, 50, and 8, in two, four, and six weeks, respectively. Revaccination took place in the seventh week after the

FIG. 1.—Virus isolation rates before and after the first and the second feedings of the trivalent live polio vaccine (Győr-Sopron county).

TABLE I.—Enterovirus Isolations by Age-group Before Vaccination

Age-group	Children Tested		Type of Virus Isolated																				Unidentified		
	No.	No. Pos.	Polio		E.C.H.O.										Coxsackie					B					
															A										
			1	3	1	2	6	7	8	11	12	14	17	19	2	4	8	9	?	2	3	4		5	
Győr-Sopron County (October 27–November 1, 1959)																									
3–23 months	34	17	1	3	1	—	—	2	1	1	1	—	1	1	3	—	—	1	—	—	—	1	—		
2–3 years ..	31	15	6	3	1	—	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—		
4–5 ..	31	12	5	1	1	—	—	2	—	—	—	—	—	—	—	3	—	1	—	—	—	—	—		
6–9 ..	36	4	—	2	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
10–15 ..	28	4	2	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Total	No.	160	52	14	11	3	—	—	8	1	1	1	—	1	1	3	3	1	1	1	—	—	2	—	
	%	100	32.5	15.6		10.0										6.9					0				
Budapest and Nine Counties (December 8–15, 1959)																									
3 months–3 years	290	50	11	2	3	2	2	4	2	—	7	3	—	—	—	—	—	1	—	1	1	9	—	2	
%	100	17.2	4.5		7.9										4.1					0.7					

primary feeding. The highest excretion rate after re-vaccination was 9.2% in the mixed 3- and 5-day samples; 7% of the 12- and 15-day specimens and 5% of the 22- and 24-day specimens yielded virus.

Fig. 2 shows the excretion rates by type and age. The low excretion rates in the age-group 10-15 years were remarkable.

The excretion rates for each of the vaccine strains had reached their peak during the first week after primary feeding. The only exception was the youngest age-group, where the peak for types 1 and 3 was shifted to the second week. In every age-group except group B the highest excretion rate was attained by the type 3 strain, and this type was being isolated most often during the whole period of observation. The peaks for the type 2 strain hardly diverged from those for the type 3 strain, with the only exception of age-group C, but the duration of the excretion was shorter—about as short as for the type 1 virus. The peaks for the latter type were remarkably low. The excretion of the type 1 and type 2 vaccine strains had stopped in 42-46 days, whereas the type 3 strain was still excreted in that period by several children in each of the age-groups except group E. After revaccination only a few children excreted virus, most of them the type 3 strain.

The excretion of Coxsackie and E.C.H.O. strains rapidly diminished after feeding the vaccine strains, probably as a result of the interfering effect of the latter.

Fig. 3 illustrates the cumulative percentage excretion curves, by age. The columns show the combinations of virus excretion by (1) the first week after primary feeding, (2) the week preceding revaccination, and (3) the fourth week after revaccination. The data on children from whom three or more specimens failed to arrive were left out of Fig. 3.

During the whole period of observation, in every age-group under study, type 3 virus was excreted most often, whereas type 1 virus was the least frequent. Group C was the only exception. Type 3 virus was isolated from 80% of the children under 6 years of age, from 73% of those aged 6 to 9 years, and from 33% of those aged 10-15 years. By subtracting the prevaccination excretion the excretion rates in the order of increasing age are modified as follows: 77, 77, 80, 67, and 25%. As regards the type 2 virus, about the same figures were obtained for the first two age-groups, but the three older groups showed definitely lower cumulative rates. Of the children aged 4 and 5 years even fewer yielded this type than type 1 virus. The excretion rates of the

FIG. 2.—Rates of virus isolation by age at various points of time during the observation period (Győr-Sopron county, trivalent vaccine).

type 1 strain in the order of increasing age were 50, 61, 46, 36, and 24%; by subtracting the prevaccination excretions the rates are 50, 40, 30, 36, and 16%.

Revaccination hardly influenced the final cumulative rates, especially in those over 4 years of age. Under 4 years a few children were found who had only yielded virus 1 or another type of poliovirus, mostly type 3 virus, after refeeding; and several vaccinees excreted the type 3 strain both before and after refeeding—for example, 13% of the children in age-group A yielded virus in the first week after revaccination (Fig. 2) without causing any rise in the corresponding cumulative excretion curve (Fig. 3, a).

As regards the first appearance of the virus in the stool, group A was somewhat divergent (Fig. 3, A). In a number of cases the second-week or the fourth-week specimens—in the case of two children even the 42- and 46-day samples—were the first positive ones for one or another type. The delay was most striking in the first appearance of the type 1 strain. This type was isolated from 15 children under 2 years of age. Five began to excrete the virus as soon as the first week, while from 8 and 2 children the first specimens yielding type 1 virus were obtained in the second and the fourth week, respectively.

The continuous rise of the cumulative curves for Coxsackie and E.C.H.O. viruses (Fig. 3) suggests that new infections with these viruses did occur in spite of

the sudden drop in the corresponding excretion rates immediately after the primary feeding (see Fig. 2).

During the observation period in the five age-groups poliovirus was found in one or more specimens of 93, 95, 90, 88, and 60% of the children, respectively. All three types of virus were excreted by 40, 43, 23, 21, and 0%; two types were obtained from 37, 44, 33, 36, and 28%; and only one type from 16, 8, 34, 31, and 32%, as shown in the column diagrams in Fig. 3. Here, too, the delayed implantation in group A is striking. In the period from the first week after primary feeding to the time of the last sampling 26% of the children in group A became new excretors of poliovirus, while the increase in the number of those excreting all three types amounted to 27%.

Some of the children examined by us were tested for neutralizing antibodies by Fornosi (1961). According to his data, kindly made available to us, the ratios of seronegative children to children tested for types 1, 2, and 3 were as follows: age-group A, 1/10, 2/10, 7/10; age-group B, 6/17, 3/17, 6/17; age-group C, 1/18, 0/18, 7/18; age-group D, 2/13, 0/13, 3/13; age-group E, 0/8, 0/8, 0/8.

Results of the Country-wide Campaign

The virus excretion rate as in relation to time is shown in Fig. 4. The prevaccination rate for enteroviruses was 17.2%, which is much more favourable than

FIG. 3.—Cumulative virus excretion during the observation period (Győr-Sopron county, trivalent vaccine).

in Győr-Sopron county six weeks earlier. The type distribution of the prevaccination isolates is shown in Table 1. After feeding the type 1 strain, the excretion rate was 42, 12, 3.2, 0.4, and 0.4% in the first, fourth, sixth, ninth, and eleventh weeks, respectively. After feeding the type 3 strain 83% of the children were positive in the first week, 48% in the fourth, and 22% in the sixth week. Type 2 virus was excreted by 59% in the first week after feeding the homotypic strain. Non-poliovirus enteroviruses were excreted by 13% before feeding, then the rate tended to decline. Cox-

sackie or E.C.H.O. viruses were excreted by 7, 8, 3, 4, and 2% of the children in the first, fourth, sixth, ninth, and eleventh post-vaccination weeks, respectively.

The cumulative excretion rates by age are demonstrated in Fig. 5. The data of those from whom more specimens than a prevaccination one had been missed were left out. Among the polioviruses, type 1 virus was excreted in the lowest rate and type 3 in the highest rate in each of the four age-groups under study. The excretion of the type 3 strain appeared to be independent of age; the cumulative excretion rate for the four age-groups varied between 81% and 95%. Unlike this, excretion of the type 1 and type 2 strains tended to decrease with age. The corresponding excretion rates were 49, 58, 46, and 32% for the type 1 vaccine strain, and 77, 62, 56, and 47% for the type 2. The final cumulative rate for the type 1 strain was attained in the first week, whereas numerous children needed several weeks to become excretors of type 3 virus.

The cumulative post-vaccination excretion curves for the Coxsackie and E.C.H.O. viruses show that several new infections occurred during the observation period.

Every child in groups A and C, and 97% of the children in groups B and D, yielded poliovirus at least in one specimen. All three types were excreted by 32, 31, 25, and 13%, and two types by 41, 48, 47, and 46% of the children in age-groups A, B, C, and D, respectively.

Fornosi (1961) found the quotients of serologically negative children for the types 1, 2, and 3 of poliovirus as follows: age-group A, 6/14, 3/14, 7/14; age-group B, 17/36, 14/36, 22/36; age group C, 15/49, 11/49, 22/49; age-group D, 3/23, 3/23, 7/23.

FIG. 4.—Virus isolation rates before and after separate feedings of the 1, 3, 2 attenuated poliovirus strains (nation-wide vaccination).

FIG. 5.—Cumulative virus excretion during the observation period (nation-wide vaccination).

There were differences in the excretion rates between geographical areas, especially for the type 1 strain. We attempted to decide whether these differences were related to the local history of poliomyelitis epidemics.

FIG. 6.—Poliomyelitis attack rates for the years 1957 and 1959, and the isolation rates of poliovirus type 1 after vaccination in ten geographical areas. Counties: 1=Szabolcs (31), 2=Pest (23), 3=Bács-Kiskun (28), 4=Fejér (24), 5=Csongrád (26), 7=Zala (29), 8=Baranya (28), 9=Vas (30), 10=Tolna (29), 6=Budapest (27). The numbers of children tested are given in parentheses.

and the highest in Tolna county (17/29). A less marked relation was found for the other areas under study, except for two, where both prevaccination morbidity and post-vaccination isolation rate were high.

Interactions Between Enteroviruses

In Győr-Sopron county the first appearance of the type 1 and type 3 vaccine strains in the faeces of children under 2 years of age was delayed. Since 38% of these young children had been found to be infected by Coxsackie or E.C.H.O. viruses, the delay seemed to be attributable to interference by these viruses. To elucidate the question, the delay was separately studied in children with and without prevaccination excretion of Coxsackie or E.C.H.O. viruses. Only children under 4 years of age were included in this study.

FIG. 7.—Cumulative virus excretion after the first feeding of trivalent vaccine, in relation to the pre-feeding carrier status. (a) No virus excretion before vaccination. (b) Excretion of Coxsackie or E.C.H.O. virus before vaccination.

C

To elucidate the question, the average poliomyelitis attack rates for 1957 and 1959 were plotted against the corresponding post-vaccination excretion rates for the type 1 vaccine strain (Fig. 6).

As seen in Fig. 6, Szabolcs county had the highest (30 cases per 100,000 population), and Tolna county the lowest average incidence (10 cases per 100,000 population) for 1957 and 1959. On the other hand, we found the lowest excretion rate (3/31) in Szabolcs county,

The comparison of the corresponding cumulative excretion curves in Fig. 7 (A) and (B) did not support the above supposition. A probable explanation of the phenomenon is presented under Discussion. Fig. 7 (B) might suggest the existence of an antagonism between the vaccine strains and the Coxsackie and E.C.H.O. viruses excreted before feeding. Among the 19 children who had excreted non-polio enterovirus, 7 continued excreting after feeding.

The use of monovalent vaccines in the nation-wide campaign provided a better opportunity for studying the possible antagonistic effect of the Coxsackie and E.C.H.O. viruses. Three children, each seronegative to the actual vaccine strain, were found who had excreted E.C.H.O. virus before feeding, and feeding was followed neither by excretion of the vaccine strain nor by serological conversion. In Cases 1 and 2 it was the type 1 vaccine strain which failed to be implanted, in Case 3 the type 3 strain; the E.C.H.O. strains which probably had interfered were identified as type 1, type 17, and type 1 strain, respectively.

Comparison of Simultaneous and Separate Feeding of the Vaccine Strains

Since the two campaigns and the schedules of the virological studies differed from each other in many respects, we had to select the comparable data before comparing the efficiencies of the two different schedules of feeding. From Győr-Sopron county only the data of children under 4 years of age were included in the comparative study, the data of the post-vaccination specimens taken at incomparable times being omitted. Since the excretion rate seemed to depend on the local history of poliomyelitis epidemics, from the nation-wide campaign we used only the data of those two areas where the incidence of poliomyelitis had approximately

FIG. 8.—Virus excretion after simultaneous (Győr-Sopron county) and separate (Fejér and Csongrád counties) feedings of the three vaccine strains. Figures above columns denote number of children tested.

agreed with that in Győr-Sopron county. The poliomyelitis attack rates per 100,000 population for the two counties were: 13.4 (1957) and 25.3 (1959) for Fejér county, and 13.0 and 18.8 for Csongrád county; for Győr-Sopron county the attack rates were 13.6 and 24.5.

The data thus selected are summarized in Fig. 8. It is shown that the excretion of the type 1 and type 2 vaccine strains was not significantly influenced by the schedule of vaccination, whereas that of the type 3 strain was much lower after feeding the trivalent vaccine than after the separate feedings. For the sake of completeness we present the average excretion rates for 10 areas involved in the virus excretion studies in

connexion with the nation-wide campaign. These were 48, 58, and 90% for type 1, type 2, and type 3 poliovirus, respectively.

Rct/40 Character Studies

Of the strains isolated in Győr-Sopron county before feeding, six type 3 strains, and all the 14 type 1 strains proved to be rct/40⁺, whereas five type 3 strains were found to be rct/40⁻ in character (Table II). Of the isolates obtained from post-vaccination samples, 20 type 1, 19 type 2, and 65 type 3 strains were examined. None of the excretors of these post-vaccination strains were harbouring enterovirus when tested before feeding.

TABLE II.—*rct/40 Character of the Poliovirus Strains Isolated from Healthy Children Before and After Vaccination*

Source of Strains	No. of Strains Tested	Virus Type	rct/40 Character			Total
			+	±	-	
Healthy children just before the oral vaccine programme	25	1	14	—	—	14
		2	—	—	—	0
		3	6	—	5	11
Healthy vaccinated children	104	1	—	—	20	20
		2	—	—	19	19
		3	21	21	23	65

Each of the type 1 and type 2 strains re-isolated from healthy vaccinees proved to be rct/40⁻ in character, whereas among the type 3 isolates rct/40⁺, rct/40[±], and rct/40⁻ strains had occurred in approximately equal numbers.

Discussion

It has been demonstrated (Sabin, 1957, 1959a, 1960; Smorodintsev *et al.*, 1959) that after feeding attenuated poliovirus strains, just as after natural asymptomatic infections, the developing immunity is not only humoral in nature; the intestinal tract also develops resistance against reinfection. Our findings in connexion with the Győr-Sopron county campaign strongly support this view. In the week after the oral administration of the trivalent vaccine the excretion rate for polioviruses was 72.5%, in contrast to the 9.2% observed in the first week after revaccination. The cumulative excretion rates for polioviruses in the four-weeks period of observation after primary vaccination, and refeeding, were 81% and 16.2%, respectively. Virus excretion after refeeding cannot be regarded as a new implantation, except in those few cases when the homotypic strain had not been excreted before, or when the excretion of a strain had stopped before refeeding and the strain reappeared thereafter. Most of the few vaccinees who yielded virus after refeeding the first time were under 4 years of age (see Fig. 3). Virus reappeared in only nine cases; the type 3 strain in six cases, and the type 1 in the others. In seven of the nine cases the reappearing strain had been isolated only once between the two feedings. This is in accordance with Sabin's (1959b, 1960) finding that the extent of subsequent intestinal resistance is dependent on the duration of the initial virus excretion.

Among the vaccine strains the type 3 strain was implanted in the highest percentage and the type 1 strain in the lowest percentage in both campaigns. The low excretion of the type 1 strain might be regarded as a consequence of the immunity acquired during the widespread epidemics in 1957 and 1959, both having been caused by the type 1 virus (Rudnai, 1958, 1960; Molnár, 1958; Földes *et al.*, 1959; Mécs *et al.*, 1961; Dömök and Molnár, 1961). This is supported by the correlation found between the local incidence of poliomyelitis during the above epidemics and the post-

vaccination excretion of the type 1 virus. A similar relation for the other two types of viruses is also possible, and its existence for the type 2 virus has been suggested by our finding in Győr-Sopron county, where this type of virus was hardly ever excreted by children over 4 years of age—that is, by those who were living when the type 2 poliovirus was predominant in Hungary (Pintér *et al.*, 1956; Földes, 1957; Molnár and Fornosi, 1957). In the case of the type 3 virus, however, excretion greatly exceeded the level expected on the basis of the preceding circulation of this type. The incidence of type 3 infections began to rise simultaneously with the decline of the 1959 epidemic (Dömök and Molnár, 1961).

The prevaccination studies in Győr-Sopron county showed that the incidence of type 3 virus approximated that of the type 1 strains late in October (Table I). Nevertheless, in Győr-Sopron county the type 3 vaccine strain was re-isolated not only most frequently but in equally high rates from 0 to 10 years of age. After feeding the monovalent type 3 vaccine 90% of the children under 4 years of age excreted this type of virus, and the isolation rate was higher for this type than for type 2 even in the youngest age-group, in spite of the fact that during 1959 only three type 2 strains were isolated by us, in contrast to the 31 type 3 and 630 type 1 strains (Dömök and Molnár, 1961).

We suppose that among the vaccinees in whom the type 3 strain was implanted there were some who had acquired natural immunity against the same type. This is in accordance with the findings of Sabin (1957), who observed that "in naturally immune subjects, resistance of alimentary tract to subsequent infection is highest for type 1 and lowest for type 3 virus." He found that 50% of young adults with naturally acquired high-avidity antibody were reinfected with the type 3 vaccine strain. Drozdov *et al.* (1960) also reported that excretion of type 3 virus was hardly hindered by naturally acquired immunity. In contrast to these, the fact that after refeeding the trivalent vaccine in Győr-Sopron county the re-isolation rate for the type 3 strain, too, was low, suggests that the feeding of this strain was also highly effective in reducing the chance of reinfection. According to Sabin (1957), "high resistance to type 3 virus among those who previously ingested type 3 attenuated virus perhaps may be related to fact that the same strain was used both times."

The relation of prevaccination serological status to the post-vaccination excretion of polioviruses was not analysed in detail. The value of such a study would be reduced by the fact that most of the children tested had been given three or four doses of Salk vaccine.

The number of virus excretors was surprisingly high just before the oral vaccine programme, especially in Győr-Sopron county, although the excretion of polioviruses may have been due to the poliomyelitis epidemic, which had not come to an end there by the end of October. However, the high level of enterovirus circulation which is regarded as unfavourable for vaccination (Sabin, 1959a, 1959b; Sabin *et al.*, 1960; Voroshilova *et al.*, 1960; Drozdov and Shirman, 1960) did not hinder the implantation of the vaccine strains significantly (see Fig. 7), at least not to the extent observed, for example, by Voroshilova *et al.* (1960). Some of our data nevertheless suggest that implantation was hindered in several cases by simultaneously harboured enteroviruses. Besides, our studies indicated, especially in Győr-Sopron county, that the vaccine strains effectively competed with the other enteroviruses

(see Fig. 2). The excretion of E.C.H.O. and Coxsackie viruses was often stopped by feeding the vaccine strains.

The comparison of the separate feeding of the three strains and the use of the trivalent vaccine was disturbed by two basic differences between the two campaigns: (1) the excretion rate for enteroviruses was higher at the time when the trivalent vaccine was fed; and (2) a single dose of the trivalent vaccine contained 100,000 CPD50 of each vaccine strain, whereas the monovalent type 3 vaccine contained 200,000 CPD50 per dose. Thus the differences observed in the implantation of the type 1 and of the type 3 vaccine strains in favour of the separate administration cannot be regarded as important. It should, however, be pointed out that our data are mass data on groups with probably few triple or double seronegative children. Thus the results cannot be interpreted as meaning that the trivalent vaccine is as effective as monovalent vaccine fed separately. On the contrary, the delay in the implantation of the type 1 and type 3 strains observed in Győr-Sopron county suggests the existence of an unfavourable competition among the vaccine strains, when fed as components of trivalent vaccine. Delay was hardly observed in the implantation of the type 2 vaccine strain, which was found to be the strongest in the competition, but it was most definitely shown by the type 1 strain, the weakest among the vaccine strains (Sabin, 1957, 1959a). The delay was most general in infancy. This age-group probably included many children susceptible to all three types, hence the chance of competition was high.

The mass oral vaccine programme carried out in Hungary has been proved highly efficient not only by the epidemiological data (Kátay, 1961) but also by the results of our 1960 enterovirus studies. After March 1, 1960, not a single virologically confirmed case of poliomyelitis occurred. During the second half of 1960 only 2 out of about 3,000 persons, either healthy or suffering from disease other than poliomyelitis, tested for virus excretion were found to be carriers of poliovirus. Both poliovirus excretors were young healthy children (3 and 4 years of age) who had received the three types of oral vaccine separately from December, 1959, to February, 1960. The two strains proved to be type 1 and type 3, respectively. The character of the isolates suggests their identity with the corresponding vaccine strains. The detailed results of our 1960 enterovirus studies will be published later.

Summary

In Hungary two extensive campaigns of vaccination with live attenuated polioviruses took place between November, 1959, and February, 1960. In Győr-Sopron county, where two doses of trivalent vaccine were fed, 141 children aged from 3 months to 15 years were repeatedly tested for virus excretion over a period of three months. During the country-wide campaign, when the three Sabin strains were fed at monthly intervals, 226 children under 4 years of age were tested similarly. Before feeding, 32.5 and 17.2% of the individuals tested in Győr-Sopron county and elsewhere in Hungary, respectively, were found to excrete enteroviruses.

After the first feeding of the trivalent vaccine the peak of the excretion rate for enteroviruses was reached during the first week. The peak of the excretion rate for polioviruses was 72.5% after the first vaccination, and 9.2% after refeeding. The corresponding cumulative rates were 81% and 16.2%, respectively. Among the three vaccine strains the type 3 strain was re-isolated

most often and the type 1 strain the least often in every age-group tested. In children under 2 years of age implantation of the type 1 and type 3 vaccine strains was delayed, probably by some interaction between them. After refeeding, the trivalent vaccine type 3 strains were isolated almost exclusively. Excretion after refeeding did not mean in every case a new implantation, since in most of the positive cases the excretion between the two feedings was continuous. The excretion rate for Coxsackie and E.C.H.O. viruses rapidly dropped after the first oral vaccination.

After separate feeding of the three vaccine strains, the isolation rate was the highest for the type 3 strain and the lowest for the type 1 strain. As regards the geographical areas under study, a correlation was found between the local incidence of poliomyelitis during the previous years and the corresponding post-vaccination excretion rate of the type 1 vaccine strain. The re-isolation rate of the type 3 strain exceeded the level expected on the basis of the prevaccination circulation of homotypic wild strains.

An attempt was made to compare the effectiveness of the trivalent vaccine and the monovalent vaccine fed separately.

The reproductive capacity at 40° C. of 25 poliovirus strains isolated from healthy persons in the week before feeding and of 104 isolates obtained from vaccinees has been studied.

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