Natural History of Herpetic Infection

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A very appropriate name for herpetic infection with its manifold clinical manifestations and varied pathogenesis is *febris herpetica infectiosa* and its subdivision: febris herpetica primaria and secundaria. The term "febris" points out the herpetic disease to differentiate it from herpetic infection. The adjectives primaria and secundaria denote the immunological condition of the organism under which the disease is manifested.

Certain epidemiological aspects of this frequently observed entity has not as yet been adequately studied, and the presentation of the natural course of the disease as appears in various text-books is very often inaccurate. This paper contains an analysis of manifested primary herpetic infection regarding its incidence, age and sex distribution, seasonal and long-term course, and the most probable sources of infection. Several epidemics in homes, children's institutions and hospital were observed.

Material and methods

This study was made in Split, a city with about 100 000 inhabitants and a comparatively centralized children's health protection; thus it was possible to comprise almost all children of a given population. The study covered only permanently resident children, regularly coming to be examined several times a year. With regard to the incidence of manifest herpetic infection two studies were performed. The first study included a group of 14 539 children followed from 1 to 9 years. After 6 years a survey was made of 4191 children of the first group belonging to the last four years of age with the insufficiently long follow-up. In all 3444 patients with the diagnosis of manifest primary herpetic infection made in the course of 11 years were observed. The standard clinical picture of herpetic gingivo-stomatitis, wich is by far the most frequent manifestation of primary infection, was the only diagnostic citerium. The source of infection was analysed only in patients allowing a good epidemiological survey.

Serology of primary herpetic infection

There are two population groups: a herpetic and a non-herpetic group. The herpetic group comprises persons with the history of manifest or subclinical infection with the herpes virus hominis. They have antibodies in their blood and may also be the carriers of the herpes virus, which manifests itself by sporadic herpetic exacerbations. The non-herpetic group, mostly children, have never been infected and have no antibodies in

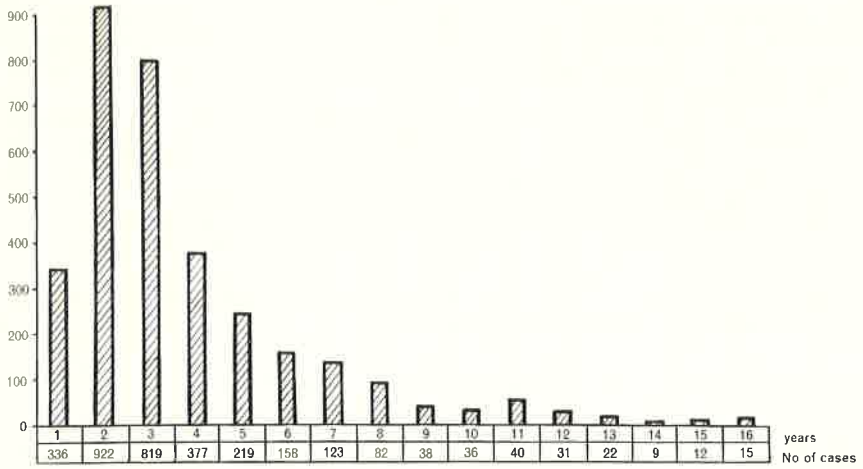

Fig. 1. Age distribution of 3278 cases of primary herpetic infection in the period 1952 to 1962 in the city of Split.

their blood. This is the susceptible population group, the so-called "population at risk". In adults contacts with the virus are considered to amount to about 70–90%, but this percentage varies according to regions and social groups [1, 8, 17]. The highest number of the non-infected population is observed at the age when inborn resistance ceases to exist, i.e. from 6 months till the end of the second year of life. All systematic investigations suggest a close relationship between age and the serologic status. Immunity to herpes virus is directly proportional to age, but there are also variations according to various populations. Immunity is also connected with the socio-economic standard. It has been proved by differences obtained in a study [6] of medical students and hospitalised patients (37%:93% positive findings), and also by a study of differences between the white and black population living under quite different health conditions (the race differences do not, of course, play any role in it). Serologically positive findings were obtained in 43% of American white children, but in 71% of American Negro children; and in 23% of African white children while in 100% of African Negro children [4, 7]. In adults there appear to be two extremes too. In Finland the herpetic group of adults living in scattered settlements under good living conditions comprised 57% at the maximum, whereas that of the agglomerated Bantu Negroes 100%. According to De Rudder, herpetic infection appears to be the infection of modern civilisation and immunity against the herpes virus may serve as a certain indicator of the hygienic standard of a population. In Yugoslavia there are no adequate studies, but by analogy with other countries, there are many reasons to believe that about 70–90% of the adult population has had previous contact with virus.

Age and sex distribution

As is seen from Fig. 1, 3278 patients were analysed according to age. There were 336 cases in the first year of life, 922 in the second, and a still high number of 819 cases in the third year, but in later age groups the incidence of infection proved to go down rapidly so that at the school age only a few isolated cases were recorded. These data are in accordance with reports from literature, the peak of infection being reported in

the second year of life. It is interesting to note that the immunological feature is indirectly proportional to the age. And it is quite logical since maximal frequency of manifested primary herpetic infection appear in the early age groups when the antibody titer is absolutely low.

In this material I was not able to confirm the assumption of ANDERSON and HAMILTON [1] that the incidence of infection is particularly low in the second half of the first year of life. I also observed an epidemic among older infants in a ward where 12 out of 21 children 6–12 months old, i.e. 57,1%, succumbed to infection. 2 infants under 6 months remained intact. This, in addition to the 336 cases observed in the second half of the first year, indicates very clearly that inborn resistance does disappear after the sixth month of life.

The analysis of cases according to sex shows a very even distribution: out of 3278 infected children 1615 were boys, and 1663 girls.

Seasonal and long-term trend

Over 3000 cases of primary herpetic infection in the city of Split in the period of 10 years were analysed according to their monthly and annual incidence. All these cases are presented in graphic form. Fig. 2 shows the general seasonal distribution which is extremely even in all seasons and all months. It can therefore be said with certainty that the incidence of herpetic infection is not affected by seasonal variations. The infection appears to be one of the most evenly distributed diseases with regard to its seasonal occurrence. Herpetic infection does not show any special long-term fluctuations either. This can be seen from Fig. 3 which shows 3443 cases recorded in a ten year period. The annual average in the city of Split amounted to 313 ± 70 cases. Minor fluctuations are of no epidemic character, they were caused by the accumulation of foci in individual families and institutions. In literature, I was not able to find any data on the seasonal incidence of herpetic infection.

Incidence of manifest infection

The study of the incidence of manifest herpetic infection involves considerable difficulties, and these studies are comparatively scarce. Complicated pathogenesis and multiple manifestations of the disease in different regions require a more specific terminology. First, distinction should be made of the percentage of primary manifest forms of herpetic infection in childhood which could be called "the attack rate" or even better, if it is obtained on the basis of short observation, the *incidence of primary herpetic disease*.

The percentage of all persons in a population that by the time of their adult life have been infected by the herpetic virus is called the *rate of the infected population*. The rate of the infected population is usually very high. No long ago RAKE stated that only one in 500 persons suffered the manifest infection, which means less than 1% [20]. MCNAIR SCOTT [18] found 38 out of 5016 children to have had herpetic disease (0.8%). A cohort study carried out by SPENCE et al. [21] in England shows that out of 950 children observed in the course of 5 years 65 were manifestly ill (6.7%).

Table 1 shows the results of a study carried out in Split in the course of several

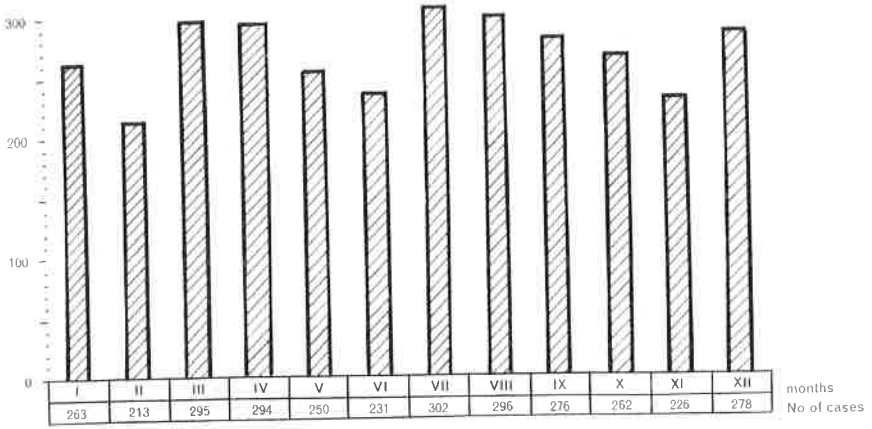

Fig. 2. Seasonal distribution of 3186 cases of primary herpetic infection in the city of Split (1952–1962).

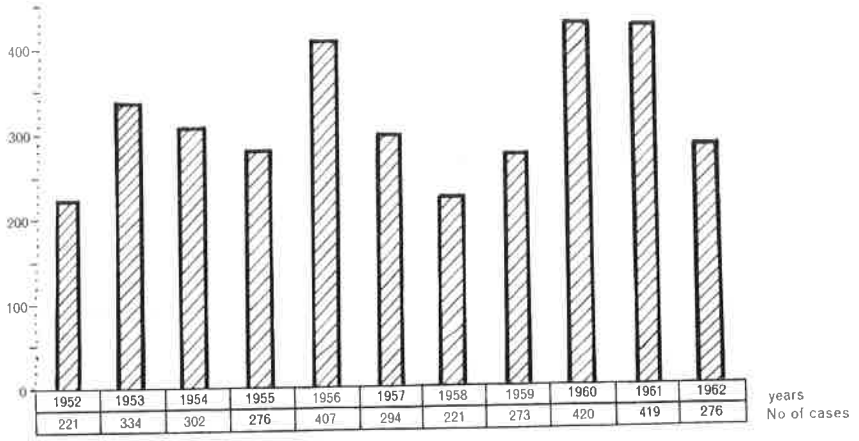

Fig. 3. Long-term trend of the incidence of primary herpetic infection in the city of Split (1952–1962). Analysis of 3443 cases.

In the first study 14 539 children 1–9 years old were observed. The total percentage of manifest infections was 10,1%. However there are striking differences regarding the age. The incidence rate is conspicuously lower in the age groups observed for a shorter time. During the period of 5–9 years it was 15%. This shows, that the number of manifested cases of herpetic infection is proportionally related to the length of observation of individual age groups. To prove this in the second phase of the study, the last 4 age groups of the first phase of the study (observed for a short time) were again surveyed in detail. The result was the prolongation of the period 5 years for all age groups. All groups showed a pronounced increase in the incidence of herpetic infection ranging almost up to 9%, so that in the second part of the study the average rate was 12,1%. If from both studies the years of life observed for more than 5 years are taken into con-

Table 1
Incidence of manifest herpetic infection in Split

Year of birth	Number of observed	Number of affected	Duration of observation	Percentage of affected
		First study in 1959		
1950	494	73	9 years	14.7
1951	554	71	8 years	12.8
1952	1892	221	7 years	11.6
1953	2460	334	6 years	13.6
1954	2070	310	5 years	14.9
1955	2152	246	4 years	11.4
1956	2119	149	3 years	7.0
1957	1509	60	2 years	4.0
1958	1289	2	1 year	0.2
Total:	14539	1467		10.1
		Second study in 1965		
1955	936	123	9 years	13.4
1956	935	131	8 years	14.8
1957	870	119	7 years	13.8
1958	1450	136	6 years	9.4
Total:	4191	509		12.1

sideration, a *frequency rate of 13,2% of evident clinical manifestations of herpetic infection is obtained.*

Under our conditions at least 10–15% of all children succumb to infection by the age of 9. The longer and the more thorough a group of children is observed, the higher is the incidence. The material observed for less than 6 years gives quite incomplete data. It is very probable that a small percentage of herpetic infection is not diagnosed at all. The reasons are well-known: either the attack of disease has occurred in a place other than the child's residence or no medical help has been asked.

Owing to some technical reasons it is not possible to present the above quoted rates per person and per year.

The upper incidence rate of primary herpetic infection in the general population has not proved to be the same as in isolated crowded children collectives, where the rate of manifest infection is much higher. Thus, Anderson and Hamilton observed 51 children in a foundling hospital and found that in the course of a year 40% of the children had herpetic disease [1]. According to my own observations on the development of epidemics in families with several family members, in children homes, and in hospitals, the incidence of manifest forms, owing to specific conditions, was considerably higher: in families up to 100%, in children homes about 80%, and in hospitals 46% of all exposed children. Massive spreading of infection, owing to a very close contact, appears to play an important role, increasing the rate of manifest infections.

Mode and source of infection

The herpes virus is ubiquitous. It is found most frequently in the sputum, but it has been isolated in the stool too. There are two possible ways of the virus transmission: a) air born infection and b) direct contact. The distribution of infection all the year round, pronounced relationship between infection and socio-economic conditions, a great number of isolated cases at minor-family foci, and no large epidemics speak very convincingly for contact transmission. In any case a close physical contact, either through the saliva or feco-orally is needed. As is well known, early childhood abounds in numerous close contacts either trough kisses or chewing utensils. Contacts between brothers and sisters and between adults and children are very frequent. In adults cohabitation is also a possible way of transmission. There are quite certainly some other factors favouring infection, such as all kinds of injuries, not only in the form of herpes traumaticus but in the first place during the dentition.

The sources of herpetic infection may be: 1. Other patients, mainly children, with primary herpetic infection. 2. Recurrent exacerbations in adults. 3. Children as healthy carriers, their percentage, according to Budingh's isolated report, being about 20% [4]. 4. Adults as healthy carriers, their percentage again according to Budingh, being about 2%.

In medical literature the percentages of contacts diverge a great deal. They are mostly based on a small number of the cases observed. Black [3], observing the highest number of patients (80), found contacts with herpetic infection only in 10%. Spence et al. [21] found the proven source of infection in 17 out of 64 patients, i.e. in 27%. McNair Scott [18], admittedly in the lowest number of patients (21), found 10 infections by, i.e. in 50%. On the basis of these analyses and the carriership observed in healthy children, the opinion has been formed that the main source of primary herpetic infection is the healthy child as the carrier.

As to the source of infection I could not rely on any card index, and for this reason I made my own survey of 581 patients with primary herpetic disease and found the source of infection in 158, i.e. in 31.5% of cases. In 80 patients (51%) the source of infection was the secondary exacerbation of herpetic infection in adults, most frequently in the form of labial herpes, but very often also in the form of recurrent aphthae. These were most often parents, relatives or nurses. In 78 patients (49%) the source was found to be another child with primary herpetic disease. At first sight adults with secondary infection and children with primary infection appear to play more or less the same role as the source of infection. But on closer observation we have found that primarily it was the secondary exacerbations in adults which provoked "the chain reaction" of primary infections in children in a given environment. True, our epidemiological survey did not find a 100% contact; no doubt, a certain number of children were infected by healthy carriers. However, one can easily understand how difficult it is to make a survey among children who already have a certain social life and may have had a great number of passing contacts. Apart from it, persons around the patients with primary herpetic disease often forget their trifle secondary infections and do not think they themselves

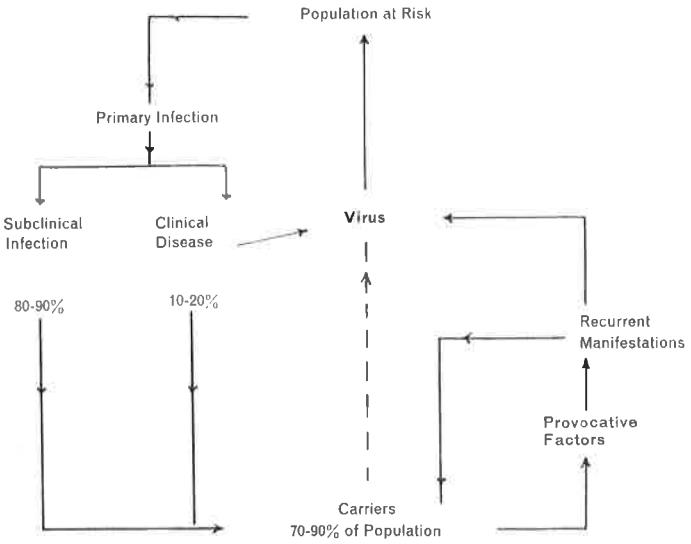

Fig. 4. Pathogenesis of herpetic infection.

might have been the cause of the child's infection; not are they likely to bring their labial herpes into any connection with the child's disease, these two formes of herpetic infection having a considerably different clinical picture. Only on a direct inquire we do get information about labial herpes, usually in parents. On the basis of these data it appears to me justifiable to assume that also in cases where there is no direct evidence, secondary herpetic infection of adults may be the primary cause of larger or smaller series of primary herpetic disease in children. My opinion is that the more carefully one looks for the cause of infection, the more frequently this cause is found to be in adults with exacerbations of herpetic infection. This opinion of mine is substantiated by frequent reports in medical literature [2, 11, 13, 15, 19] relating to eczema herpeticum and herpes generalisatus neonati. These disorders are looked upon much more seriously by both physicians and parents, and their primary cause is far more frequently tried to be found in recurrent herpes in adults. In my opinion, *adults are the mass reservoir of the virus and through their secondary exacerbation, the main cause of infection in children.*

On the basis of these assumption of the cause of infection and with regard to the incidence rate already mentioned, it appears necessary to introduce certain changes into RAKE's classical scheme of the pathogenesis of herpetic infection. In the moment I want to point out the possibility of infection in a susceptible person directly from a patient with a primary or secondary herpetic disease, or potentially from a healthy carrier. The ratio manifest and inapparent infection is changed (Fig. 4).

Epidemics of herpetic infection

So far very few epidemics of herpetic infection have been reported, so that the infective character of the disease is often overlooked. I have had the opportunity of following several epidemics of this disease in various

environments: in families, hospitals, and such institutions as children homes, schools, public nurseries, foundling, etc. [12].

1. Epidemics in families

In 1938, in the addendum to his paper [5], the virologist BURNET, who has greatly contributed to modern approach to the epidemiology of herpetic infection, set forth an interesting example of family epidemic observed by the general practitioner A. P. DERHAM. The mother and the houshelp had secondary labial herpes and infected two children with the incubation period lasting 4 days. The children developed primary stomatitis herpetica. Five days later the third child fell ill.

In 1941, MCNAIR SCOTT [16] described 3 family epidemics. In one epidemic 5 children and in the other two 3 children were affected. In 1944 CHILTON reported a herpetic infection in a Negro family with 6–8 family members [18].

In our study from group of 158 patients with the proven source of infection 12 families with more than two infected members were submitted to analysis (Fig. 5). I found 9 families with 3 members and 3 families with 4 members affected. In these families not a single child was left without showing manifest infection. In 12 families I found the primary source among adults with recurrent herpes six times. Once, admittedly, these were recurrent aphthae in the fathers mouth, and another time it was labial herpes in an older child. In 5 families the cause of the epidemic was a case of primary infection in other children of the same family or of the family co-tenants. It has to be pointed out that when the diagnosis of herpetic epidemic is established only in the third or fourth case, it is very hard to make a retrograde detection of the primary cause of the epidemic which might have been quite unconspicuous. In my material of family epidemics 100% of children in the families observed showed manifest infection. However, the cases observed are too few to give an answer which actual attack rate is. To provide an answer to it, further observations on a far more abundant material are needed.

2. Hospital epidemics

Hospital epidemics relate to contacts in maternity wards where the mother, by her genital organs or by labial herpes, may affect her own newborn which develops a generalized infection, almost regularly with a fatal issue. These cases, however, are rare, because the newborn child is protected by inborn resistance. Exceptions are premature children which succumb to infection most frequently. In Yugoslavia no such cases have been reported. Other dangerous places are dermatology departments hospitalising infants with exzema. In 1955 PUGH, DUDGEON, and BODIAN [19] described a contact epidemic "eczema herpeticum Kaposi" in 4 patients who in succession fell ill in 3–8 day intervals. Their observation that also the patients nurses were affected by them, developing herpetic vesicopustules on hands, is very interesting. In Yugoslavia S. PURETIĆ (personal communication) observed 2–3 cases of eczema herpeticum succeeding each other at the Dermatology clinic of Zagreb University Hospital.

At the children department of our hospital we had the opportunity of following an epidemic of primary herpetic disease. The diagram (Fig. 6) shows the course of the epidemic in 17 children. Their age, date of admission, the beginning and the end of the disease. The epidemic started with the admission of two children (M. S. and Z. J.). In one child the disease already existed on admission, while the other fell ill on the second day after admission. "Housing" conditions at the ward were difficult, because in the middle of summer, two patients shared one bed. Almost all infants suffered from either light or serious forms of dystrophies and enterocolitis. The children were 4 months to 2 years old. In three rooms 37 children up to 2 years old were exposed. All the children were at the age when they were practically considered as having had no contacts with virus

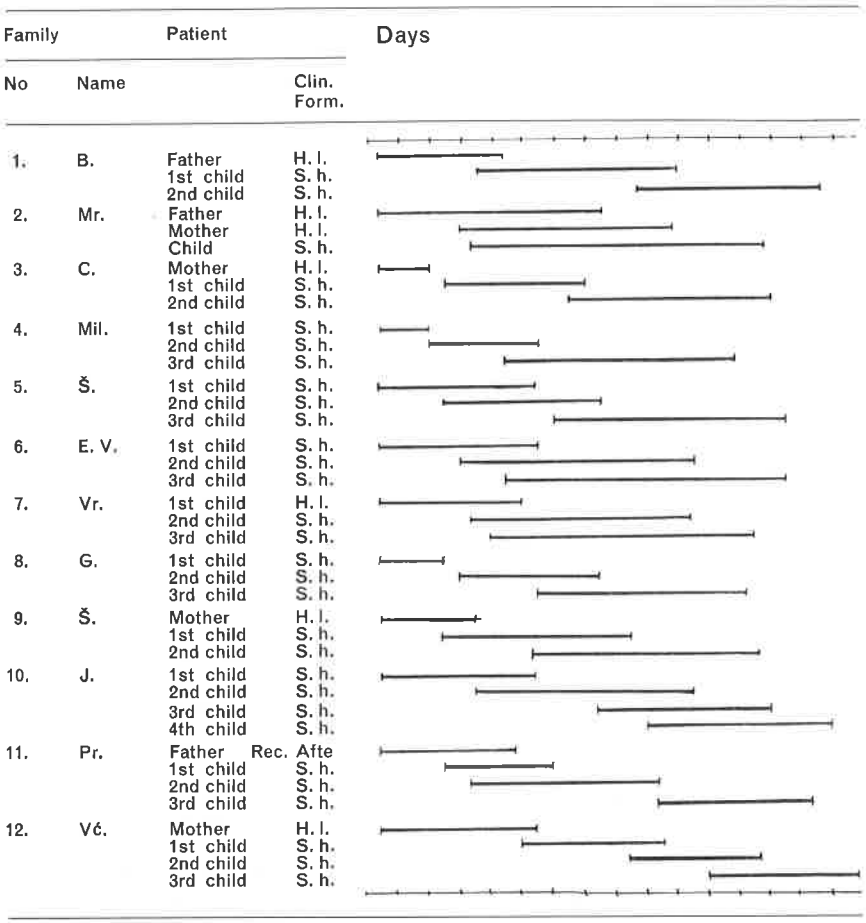

Fig. 5. Family epidemics of herpetic infections. S. h. = Stomatitis herpetica. H. l. = Herpes labialis. |—| = Duration of illness.

(only 3 from 14 to 24 months). During this epidemic a total of 17 children, i.e. 46% of all exposed children, developed manifest forms of infection. If two infants with inborn resistance under 5 months of age and one discharged somewhat earlier are exluded, a rate of almost 50% is obtained. Almost all children developed typical gingivo-stomatitis with a clear clinical picture. One of them, in addition to serious stomatitis (K. M.), had a pronounced herpetic keratoconjunctivitis. Two children, in addition to stomatitis, developed herpetic vesicopustular efflorescence on the face and trunk skin. Only one child (D. B.) had only herpetic vesicopustules (herpes cutis) on the skin, without changes in the mucosa.

The epidemic first broke out in ward 1 with the two cases brought from outside; in this ward it affected in the large number of children (up to 60%). Later the epidemic was transmitted to wards 2 and 3 where it lost in its intensity, so that in these wards

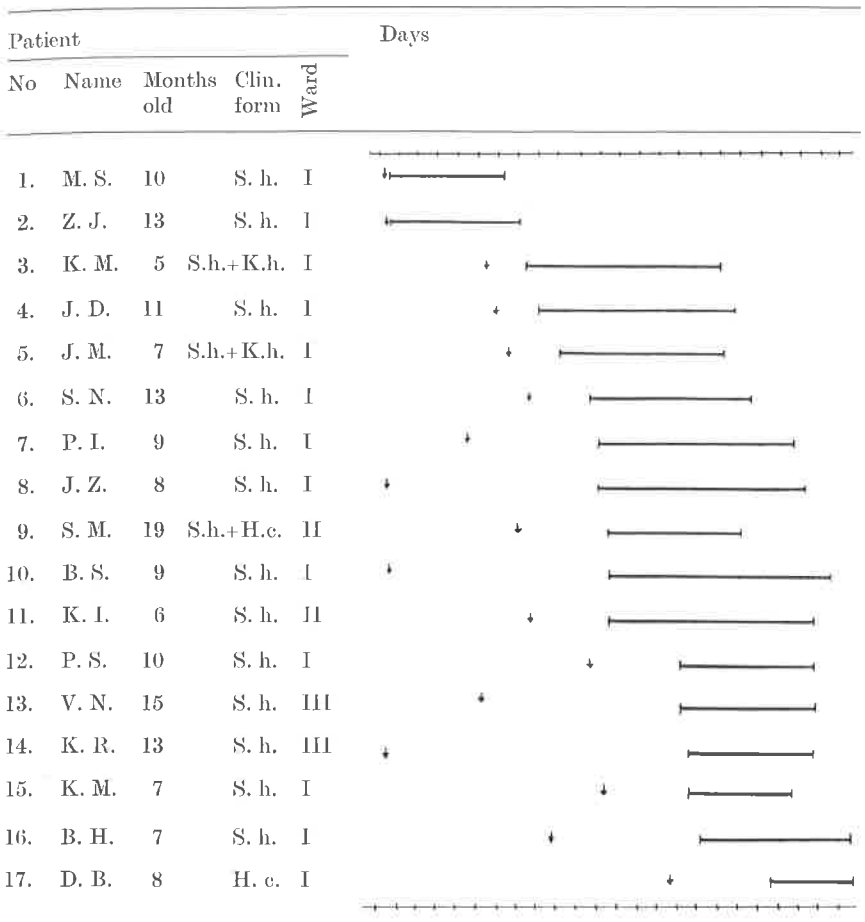

Fig. 6. Hospital epidemic of herpetic infection. S. h. = Stomatitis herpetica. H. c. = Herpes cutis. K. h. = Keratitis herpetica. |—| = Duration of illness, ↓ = Admission to Hospital.

a considerably lower number of children were affected. No doubt, this was due to prophylactic biologic and hygienic-preventive measures, mostly to the improved housing conditions, a better control of the utensils used, isolation, etc.

3. Institutional epidemics

I observed three epidemics in a children home (Fig. 7) in children 1–3 years old. Clinically there was always herpetic gingivostomatitis. In the first two epidemics, the children's nurses with labial herpes were the source of infection. The first epidemic affected 6, the second 5 and the third 5 children. They all shared the same ward. The epidemic did not spread to other wards. No special prophylactic measures were used.

Patient No		Month old	Clin. form.	Days
I. Epidemic 1956				
1.	Nurse		H. l.	
2.	Child	20	S. h.	
3.	Child	28	S. h.	
4.	Child	24	S. h.	
5.	Child	30	S. h.	
6.	Child	19	S. h.	
7.	Child	20	S. h.	
II. Epidemic 1957				
1.	Nurse		H. l.	
2.	Child	25	S. h.	
3.	Child	15	S. h.	
4.	Child	33	S. h.	
5.	Child	18	S. h.	
6.	Child	20	S. h.	
III. Epidemic 1957				
1.	Child	28	S. h.	
2.	Child	20	S. h.	
3.	Child	19	S. h.	
4.	Child	32	S. h.	
5.	Child	23	S. h.	

Fig. 7. Institutional epidemics of herpetic infections. S. h. = Stomatitis herpetica. H. l. = Herpes labialis. |—| = Duration of illness.

Other patients had either a subclinical infection or had had contact with the virus. During these epidemics almost all children from these wards were affected, so that the morbidity rate in the first epidemic was 75%, in the second 71%, and the third 83%. All other patients appear to have had either subclinical infection or were previously immunized by the natural way. Both assumptions are feasible, because these were children up to 3 years old, belonging to the economically poor social group. It was not possible

to obtain any data on some herpetic infection in the past, because most children were without parents.

What is very instructive in these epidemics is the fact that nurses with labial herpes, engaged in children's care, may be the cause of primary herpetic disease in children. The percentage of manifest infections in the most exposed children in the attacked wards was very high: 71–83%. The course of the disease in these predominantly healthy children was somewhat shorter and more benign than in hospitalised dystrophic children.

The incubation periods in all these epidemics ranged from 2 to 11 days. The mean being 5.5 days with standard deviation of 1.6 days. This is in full agreement with my previously published study [9]. On the basis of a total of 139 secondary infections, in which it was possible to rely the parents information regarding the length of the incubation, the incubation ranged from 2 to 12 days with the arithmetic mean of 6.1 and the standard deviation of 2.6 days.

Conclusion

In the course of 6 years 14 532 children of the city of Split had been observed as regards the incidence of manifest herpetic infection. Separately 3444 patients had been surveyed. It was found that the incidence peak was in the second year of life, while in the first 6 months there were no manifest cases. The incidence gradually decreases as the child grows up. A high number of cases in the second half of the first year of life is in disagreement with the established opinion that this age is free from this disease. In hospital epidemic the attack rate was 57% of children aged 6–12 months. The occurrence of primary herpetic disease is not influenced by seasonal variations. There is no uneven distribution as regards its long-term incidence either.

The incidence of manifest herpetic infection in a large group of children observed for a long time was 10–15%. This is the highest rate reported so far in a general population and based on a comparatively high number of the patients duly observed. The epidemiological survey as regards the source of infection was made in 581 patients; the source was found in 31% of cases. The primary cause of one or more infections in children was most often proved to be the adult relatives or nurses with the exacerbation of labial herpes, which means that adults are the main active reservoir of the virus and with their secondary infections, the main source of infection in children.

An exceptional situation was observed in crowded children collectives where the epidemics of herpetic infection where rarely reported. Nine minor family epidemics, 3 institutional, and one major hospital epidemics were observed. In all these epidemics a high rate of manifest infections (46–100%) were evidenced. The primary source was always the secondary herpetic infection of adults. The divergencies of these results as regards the conditions in children's populations are explained by the effect of massive infection in isolated collectives.

The incubation period in all these epidemics and in sporadic cases (139 in all) was 2–12 days with the mean of 6.1 days and the standard deviation of $\pm$ 2.6 days.

Zusammenfassung

Im Verlaufe von 6 Jahren wurden 14 532 Kinder der Stadt Split im Hinblick auf die Häufigkeit manifester Herpesinfektionen untersucht. Außerdem wurden 3444 Kranke mitberücksichtigt. Das Häufigkeitsmaximum entfällt auf das zweite Lebensjahr, während in den ersten 6 Monaten kein einziger manifester Fall beobachtet wurde. Mit dem Alter geht die Häufigkeit allmählich zurück. Die große Zahl der manifest befallenen Säuglinge des zweiten Lebensjahres steht im Widerspruch zu den herrschenden Meinungen, daß diese Altersstufe verschont bleibt; in Spitalepidemien erkrankten 57% der 6 bis 12 Monate alten Kinder. Die primäre Herpeskrankheit bevorzugt keine Jahreszeit und keinen Jahrgang seit 1952.

Die Häufigkeit manifester Erkrankungen beträgt 10–15%; dies ist die höchste bisher beschriebene Zahl. Unter 581 darauf hin untersuchten Kranken wurde in 31% die Infektionsquelle nachgewiesen. Die häufigste Ursache ist der Herpes labialis von erwachsenen Verwandten oder Krankenschwestern; dies bedeutet, daß die Erwachsenen das wichtigste Virusreservoir sind und ihre sekundäre Infektion die wichtigste Quelle der Ansteckung der Kinder.

In Kollektiven, wo die Kinder zusammengepfercht sind, kamen Herpesepidemien selten vor. 9 kleine Familien-, 3 Heim- und eine große Spitalepidemie wurden beobachtet. In allen diesen Epidemien war die Zahl der Manifesterkrankten groß (46–100%). Immer war eine sekundäre Erwachseneninfektion die Quelle der Ansteckung. Die erwähnten Unterschiede in der Häufigkeit der Manifesterkrankungen erklären sich aus der massiven Infektion in isolierten Kollektiven.

Die Inkubationszeit bei diesen Epidemien und bei den sporadischen Fällen (131) betrug 2–12 Tage mit einem Mittel von 6,1 Tagen und einer Standardabweichung von $\pm$ 2,6 Tagen.

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