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OBSERVATIONS ON THE CHARACTER OF AN EPIDEMIC OF INFLUENZA AND ON THE EFFECTS OF VACCINATION

The authors made a study of the character of an epidemic of influenza observed in Finland in the spring 1953 and of the effects of vaccination in 7 commercial or industrial concerns, in which 858 workers were vaccinated, while 751 served as a control group. The vaccination was performed at the beginning of the epidemic, which was actually too late and therefore even theoretically immunity had no possibility to develop in all cases. In the material as a whole, there was no marked difference between the groups of those who were vaccinated and the controls (7.8 versus 9.7 per cent). Influenza contracted two years earlier had no clear immunizing effect. The epidemic of 1953 must be considered mild. As regards complications, pneumonia occurred in only 2.5 per cent, sinusitis in 2.7 per cent, and otitis media developed in 2 cases. Antibiotics were used in only 10 per cent of the cases, which must be regarded as a satisfactorily small proportion, considering the occurrence of complications in almost 6 per cent of the patients.

On the basis of the present study, vaccination against influenza by using the commercial vaccine has not as yet given such results in our conditions as has been hoped for.

Vaccination against influenza has been in use for more than ten years. In 1943, a large team of investigators made an extensive study in order to assess the efficacy of the vaccination. The study covered a material of more than six thousand vaccinated men and a control group of equal size. The latter were given an injection of saline. When examining the patients, the physicians were unaware of their distribution to the above groups. The results were rather stimulating. In the vaccinated group 2.22 per cent contracted influenza, whereas the percentage was 7.11 in the control group (*Members of the Commission on Influenza* etc.). During an epidemic caused by the B virus in 1945, *Francis, Salk,* and *Brace* carried out an investigation, in which the morbidity was 1.15 per cent among those vaccinated and 9.91 per cent among the controls. During the same epidemic *Norwood* and *Sachs* obtained as corresponding morbidity figures 1.94 and 8.23

Table 1.

Some previous studies of the effects of influenza vaccination on morbidity

	Year of publication	Vaccinated		Unvaccinated		Virus	
		Total	Morbidity %	Total	Morbidity %		
Commission on Influenza	1944	6.263	2.22	6.211	7.11	A	
Francis, Salk, Brace . . .	1946	600	1.15	1.100	9.91	B	Same epidemic
Norwood, Sachs	1947	366	1.94	4.280	8.23	B	
Francis, Salk, Quilligan	1947	10.328	7.19	7.615	8.09	A_1	Same epidemic
Sigel, Shaffer, Kirber, Light, Henle	1948	464	54.00	57	49.00	A_1	
van Ravenswaay	1948	237	20.2	284	27.8	A_1	
Bernstein, Reber, Sheris	1952	515	4.5	585	8.4		
Yeager , ...	1952	847	1.77	1.952	9.4	A_1	

per cent respectively. The results (cf. Table 1) seemed thus relatively promising, until during an epidemic in the spring of 1947 in the United States the vaccination unexpectedly proved ineffective. The most extensive material covered 37,000 vaccinated subjects and a control group of equal size. The incidence infections of the upper respiratory tract was the same in both groups (BAETJER 1948). *Francis, Salk* and *Quilligan* arrived in their studies at the conclusion that the epidemic was caused by a strain of virus markedly differing from those contained in the vaccine. They state: »In view of the laboratory studies indicating that the antibody titer for the new strain was essentially the same in vaccinated and unvaccinated persons, it is not surprising that the amount of illness was practically the same.« The morbidity was 7.19 per cent among those vaccinated and 8.09 per cent among the controls. This so-called A_1-virus has thereafter been included in most vaccines. In other publications dealing with the same epidemic the morbidity figures are higher, but nevertheless almost the same in both groups. This may depend partially on the circumstance that these studies include more cases of other virus infections of the upper respiratory tract. In the material of *Sigel* et al., the morbidity was 54 per cent among those vaccinated and 49 per cent in a small control group. They too came to the conclusion that the virus causing the epidemic differed in its antigen from those previously observed. In another material the

morbidity was 20.2 per cen among those vaccinated and 27.8 per cent among the controls (VAN RAVENSWAAY 1948). It is interesting to note that after about half a year the same virus occurred as an endemic with a morbidity of only about 5 per cent. This was observed when a serological study was made of patients treated under the diagnoses: nasopharyngitis, laryngitis and bronchitis (SALK and SURIANO 1949). Three years later A_1 caused once more an epidemic in the United States. This time a vaccine containing the said virus gave a good protection: 1.77 versus 9.4 per cent (YEAGER 1952).

The failure of the vaccination in 1947 caused a lively exchange of opinions, which shows the difficulties to be overcome when aiming at a really effective prophylaxis against influenza. Some investigators put forward the view that the influenza virus has possibilities of an unlimited number of mutations and when viruses cultivated from earlier epidemics are used for the vaccines, one is always fighting against a disease once previously contracted. Some other investigators again consider that the facts are against a continuous and unlimited variation of the virus (SALK, LAURENT and BAILEY 1951). They stress that during twenty years after the discovery of the influenza virus only two immunologically quite different types, A and B, have been found. The antigenic variants of these, discovered either in nature or in the laboratory, differ only little from the original culture. They are convinced that it is possible to chose a group of strains, the antigenic properties of which correspond to all or almost all known A and B viruses, and to make a vaccine from them. Attempts have been made to increase the efficacy and to prolong the effect of an influenza vaccination with the aid of socalled adjuvants, i. e. by making an emulsion of the concentrated vaccine in mineral oil. Preliminary experiments on monkeys and human subjects showed that such a vaccine stimulated the formation of antibodies considerably more effectively than an ordinary vaccine in saline (SALK, LAURENT and BAILEY 1951).

The great importance of an efficient prophylaxis against influenza is evident when considering a pandemic like that of 1918–20. In some countries, for instance in the Netherlands, equally severe influenza has been observed in a number of cases also during recent years, the disease being characterized by a fulminant course and by the death of the patient within 1 or 2 days after the onset of the symptoms. In such cases, influenza viruses of the A and B types have been isolated from the lungs of the patients, and regularly also various bacteria, often in pure culture. Although the latter proved penicillin and streptomycin sensitive, massive doses of the said antibiotics have not altered the course of the illness. As is well known, the morbidity and the loss of working days due to even an ordinary epidemic are greater than in any other disease.

Vaccination

When an influenza epidemic was expected and at its onset mass vaccination against influenza was performed in 7 commercial and industrial concerns in Helsinki. During the period 2. 2.–19. 2. 1953 851 persons were vaccinated, while 745 served as a control group. 95 per cent of the vaccinations were made during the period 2. 2.–12. 2. 1953. The epidemic spread to Finland from Central Europe, where the causative agent had been isolated at the end of January and identified as a virus of the A_1 type. Therefore, commercial vaccine* was ordered and obtained, containing two strains of the A_1 virus, one isolated during the abovementioned epidemic of 1947 and the other during an epidemic in Liverpool, in 1951. Moreover, it contained the B type strain of Bon. 0.3 ml of the vaccine was injected intracutaneously into the skin of the shoulder region. The dose to be used subcutaneously is 1 ml. All who wished, except for those suffering from asthma or clearly allergic to eggs, were vaccinated. The intracutaneous administration is more advantageous than the subcutaneous route, because it causes less side-effects and is equally effective and more economical than the latter (DIGNAM 1947; BRUYN, MEIJKLEJOHN and BRAINERD 1949).

The side-effects caused by the vaccination were slight. They were observed in 21.1 per cent of cases. The majority of these patients suffered monosymptomatically from some slight symptom. Because many contracted influenza soon after the vaccination, and it was thus difficult to decide whether the symptoms were caused by vaccination or influenza, only those were considered in judging the side-effects who remained free from influenza. The frequency of the side-effects was of the same magnitude as in Dignam's material, and considerably lower than in those of some other investigators (NORWOOD ans SACHS 1947; BERNSTEIN, REBER and SHERIS 1952). The side-effects of the vaccination are listed in Table 2.

Table 2.

Side-effects of the vaccination

Fever	6.0 %
Headache	5.7 %
Nausea	6.4 %
Oedema	4.4 %
Rhinitis	1.6 %
Fatigue and vertigo	1.6 %

(Pain in shoulder and arm was reported by only 5 patients, and one suffered from pain in the joints.)

* supplied by Philips-Roxane.

CHARACTER OF THE EPIDEMIC AND EFFECT OF THE VACCINATION

In many cases it is clinically very difficult to differentiate influenza from other related virus diseases, particularly from the so-called rhinitic fever, for which the names infectio acuta naso-pharyngo-trachealis and common cold are used (POTTER 1951; SALK and SURIANO 1949).

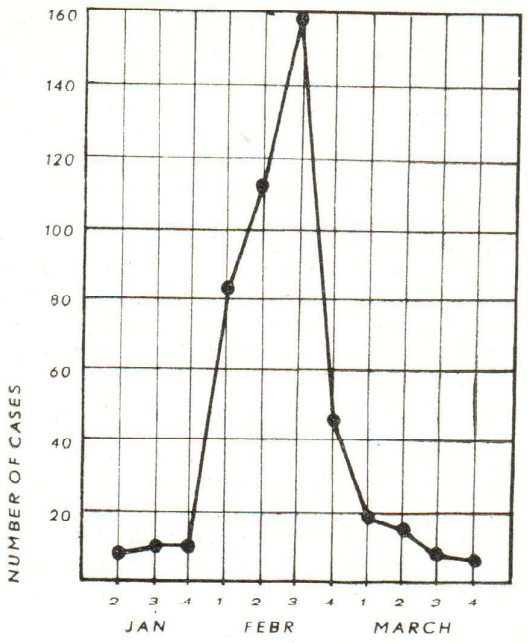

Fig. 1. The number os cases per week.

In this respect, exact results are achieved only with the help of serological tests. During the culmination of the influenza epidemic the morbidity was so high that there was no possibility to observe all the patients personally. For these reasons, all acute infections of the upper respiratory tract were included in the material, except for cases diagnosed with certainty as something else than influenza, e. g. as tonsillitis, pneumonia, etc. Because the vaccination against influenza has no effect on common cold, the employed selection of the material tends to reduce the difference between those vaccinated and the controls. During the epidemic the impression was obtained that an active common cold prevents an infection with influenza, but no detailed study was made of

this relationship. The same observation has been made also previously (POTTER 1951). This may possibly depend on an interference phenomenon between the viruses, the existence of which between various types of influenza virus has been demonstrated by *Andrews* (1948) in animal experiments. The phenomenon is not immunological.

The first cases of influenza were diagnosed on February 4th and 5th. On February 6th the number of those who had contracted the illness was so great that the onset of an epidemic could be regarded as certain. The daily number of new cases increased rapidly. Before the epidemic, from 6 to 10 persons every week contracted acute infections of the respiratory tract. The corresponding figure was 41 in the first week of February. During the next week the number rose to 112. The epidemic reached its culmination in the third week, when the number of cases was 158. After this, a steep fall ensued. During the last week of February 46 persons contracted the illness. In the first two weeks of March the morbidity was still slightly above the normal (19 and 16), but it fell after it to 5–6 (Fig. 1).

The general morbidity was relatively great during the epidemic. Approximately 30 per cent of the personnel of the concerns under investigation suffered during it from an acute infection of the respiratory tract, of the type of influenza. When examining the group of those vaccinated and the control group as a whole, no difference could be observed between them. After the vaccination, approximately 7–10 days elapse before immunization has developed. During this interval, many contracted the disease, some already before the vaccination. In order to be able to assess the effect of vaccination on the morbidity, those who became ill later than 10 days after the vaccination were collected into a separate group. A control group was chosen from those who were not vaccinated and who contracted the illness later than 10 days after a mass vaccination had been performed in the concern. From 851 vaccinated subjects, 67 became ill, and from 751 unvacci-

Table 3.

Morbidity among the vaccinated and the unvaccinated

	Total	A		B		A	B
		Contracted influenza	Morbidity per cent	Contracted influenza more than 10 days after vaccination	Same per cent	Absence days per patient	Same among group B
Vaccinated	858	258	30.1	67	7.8	3.1	2.2
Controls . .	751	230	30.6	73	9.7	3.4	3.2
Total	1609	488	30.4	140		3.2	

nated controls, 73 contracted the disease after the said interval. In the former group, the proportion was 7.8 per cent, and among the latter 9.7 per cent. The difference is not great.

When dividing the material according to whether the patient had suffered from influenza in 1951 or not, the following result is obtained: among those who were ill in 1953 27.9. per cent had contracted influenza also in 1951. Among those who remained healthy during the recent epidemic only 21.4. per cent had suffered from influenza in 1951. As may be remenbered, the epidemic of 1951 was also caused by a virus of the A_1 type. The immunity due to illness had thus disappeared in less than two years.

Influenza occurred generally with typical symptoms, and therefore they will not be subjected to a detailed examination. However, an observation deserves being mentioned. The more common and more intense a symptom of influenza, the earlier it occurred in the course of the disease (Table 4).

Table 4.

The symptoms, their order of appearance and frequency

	Order of appearance	Per cent	
Fever	1	91.2	
Headache	1	76.3	86.5 %
Pain in the muscles	2	61.8	
Cough	3	67.5	
Rhinitis	4	69.7	88.1 %
Sore throat	4	35.6	
Nausea	5	25.4	31.9 %
Diarrhoea	5	13.3	

The typical course of the illness was in the present material as follows: The illness started acutely with severe general symptoms. They were accompanied by catarrhal symptoms which were relatively slight as compared with the general condition. Slight gastrointestinal disturbances occurred at a fairly late stage and inconstantly. It is clear that considerable deviations from the above occurred in individual cases.

The duration of increased temperature was on an average 3.7 days in the material as a whole, and that of absence from work 3.2 days. Among those who contracted the illness later than 10 days after the vaccination the mean duration of fever was 2.7 days and that of absence from work 2.2 days; in the analogous control group the corresponding figures were 3.2 days and 3.2 days.

Relatively few complications of influenza were observed: pneumonia 12 (2.5 per cent), sinusitis 13 (2.7 per cent), and otitis media 2 cases. There were no fatal cases.

Among the 488 cases of infection 92 had obtained some kind of chemotherapy (sulphonamides or antibiotics or both). 48 patients had taken antibiotics, the majority penicillin. Aureomycin had been given to 12, chloromycetin to 2, and terramycin to 1 patient. Considering the 27 cases of complications and a suspicion of complications in a number of the other patients, these drugs had been used with wrong indications quite rarely. This may have been due also to propaganda against the chemotherapy made during the epidemic.

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SADRŽAJ

Autori su proučavali karakter epidemije influence, koja se pojavila u Finskoj u proljeće 1953., kao i efekt vakcinacije, koja je provedena u 7 trgovačkih i industrijskih poduzeća na 858 radnika, dok je 751 radnik iz tih poduzeća služio kao kontrolna grupa. Vakcinacija je provedena na početku epidemije, a to je već u stvari bilo prekasno i zato se čak ni teoretski imunitet nije u svim slučajevima postigao. Između vakciniranih radnika i kontrolne grupe, koja nije bila vakcinirana, nije bilo značajne razlike (7,8 prema 9,7).

Influenca u 1953. godini treba da se smatra blagom. Što se tiče komplikacija, utvrđene su pneumonije samo u 2,5%, sinusitis u 2,7%, a otitis media razvila se u dva slučaja. Antibiotici su upotrebljeni samo kod 10% od oboljelih radnika. To se može smatrati vrlo malim procentom s obzirom na procenat komplikacija, koje su se pojavile kod 6% oboljelih.

Na temelju ove studije autori izvode zaključak, da vakcinacija protiv influence komercijalnom vakcinom nije dala one rezultate, koji su se očekivali.