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## EVALUATION OF THE EFFEC- TIVENESS OF ANTI-INFLUENZA VACCINATION\*

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EVER SINCE the first influenza virus was isolated, a number of research workers have attempted to evaluate the effectiveness of vaccines derived from it. The results of these experiments have been very inconclusive. Some consider that the use of the vaccine has greatly reduced the incidence of cases of respiratory disease, while others think that the attack rate has not been significantly different between controls and vaccinated persons.<sup>1, 2</sup>

Moreover, in the opinion of those who have not merely noted the total incidence of respiratory disease, but also made a distinction between general respiratory disease and true influenza, vaccination with a vaccine of antigenic structure identical with that of the virus responsible for the epidemic has significantly lowered the incidence of influenza in those receiving it.<sup>3-5</sup>

With these studies in mind, we attempted during the course of the winter of 1954-55 to assess in our area the degree of protection conferred by a polyvalent anti-influenza vaccine. §

### METHOD OF PREPARATION OF VACCINE

The vaccine was prepared by us in the laboratories of the Institute of Microbiology and Hygiene of the University of Montreal. Preparations included the following steps:

We inoculated each type of influenza virus into the allantoic cavity of chick embryos 11 days old. Embryos inoculated with strains of type A were incubated for 48 hours at 37° C. Those inoculated with a type B were kept at 35° C. for 96 hours.

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After this period of incubation the allantoic fluid was collected aseptically, and the virus which had multiplied within it was purified and concentrated by centrifugation. After treatment with formol 1 in 4000, the agglutinating power of each monovalent vaccine was adjusted by dilution to 500 units per c.c.

The strains A/PR8/1934, A/FMI/1947, A/Cuppett/1950 and B/Lee/40 were used to prepare vaccine and the latter submitted to control tests in accordance with "Minimum requirements: influenza virus vaccines".<sup>6</sup>

The four monovalent vaccines were mixed in following proportions: PR8, 22.2%; FMI, 22.2%; Cuppett, 22.2%; Lee, 33.3%.

Control solutions were prepared by the same procedure except that the stage of infection of the embryos was omitted. The degree of opalescence of the vaccine was used as a measure of when the moment to dilute the normal allantoic liquid was reached.

### VACCINATED GROUPS

Epidemic influenza is usually very unpredictable. It is impossible to predict what group it will affect and what area it will spare. We therefore decided in the winter of 1954-55 to make up four groups of volunteers at random, in an attempt to measure the protection conferred by our vaccine on those vaccinated.

#### *Group 1: At the Psychiatric Hospital*

This institution has 6000 patients: 2862 were given the vaccine and 748 the non-virulent liquid (placebo); 1077 served as non-vaccinated controls. In essence this is a very closed community; however, because of the personnel who live outside, the visitors, and those patients who are allowed out, this hospital has frequent and multiple contacts with the population of the city of Montreal.

#### *Group 2: Civil Service, City of Montreal*

A group of 558 civil servants were given the vaccine and 476 the placebo fluid; 2466 individuals were used as non-vaccinated controls.

*Group 3: A Montreal Factory*

The vaccine was given to 313 workmen and the placebo solution to 277 others.

*Group 4:*

For a fourth experimental group, we chose a semi-rural area, Montmagny, situated 40 miles down the river from Quebec. The vaccine was administered to 1525 children and 236 adults; 558 children and 195 adults were given injections of placebo.

secure an effective dispersion of the vaccine aerosol into the upper respiratory tract, and in order to maintain the pressure at a constant level in all subjects, the apparatus was connected with an oxygen reservoir. We introduced paper cones with tips cut off into the nostrils; this made it possible to introduce without contamination the ends of glass tubes attached to the vaporizer (Fig. 1). Finally, to make sure that the vaccine penetrated thoroughly, we asked each person to take five deep breaths.

TABLE I.—NUMBER VACCINATED IN EACH GROUP

	<i>One injection of vaccine</i>	<i>Two injections of vaccine</i>	<i>One injection of vaccine; revaccination with aerosol</i>	<i>Placebo</i>	<i>Not vaccinated</i>	<i>Totals</i>
1. Mental hospital . . . . .	1114	890	858	748	1077	4687
2. Civil service, City of Montreal . . . . .	558	—	—	476	2466	3500
3. Montreal factory . . . . .	313	—	—	277	—	590
4a. Montmagny—children . . . . .	131	633	761	558	—	2083
4b. Montmagny—adults . . . . .	—	—	236	195	—	431
	2116	1523	1855	2254	3543	11,291

Study of Table I will show that we divided the four groups into subgroups. The 1st, 2nd and 3rd subgroups were given, either in October or in November, 1 c.c. of vaccine subcutaneously, while the fourth subgroup was given 1 c.c. of the placebo solution, identical in appearance with the real vaccine. It was impossible to distinguish the placebo from the vaccine; the vials of one or the other could be identified only by a number which was unknown both to the administrators and the vaccinated subjects.

In February, persons in the second subgroup were given a second injection of vaccine, while those in the third subgroup were given their booster dose by the nasal route (inhalation). For this purpose we used a Vaponefrin apparatus which discharges droplets 1-2  $\mu$  in diameter. In order to

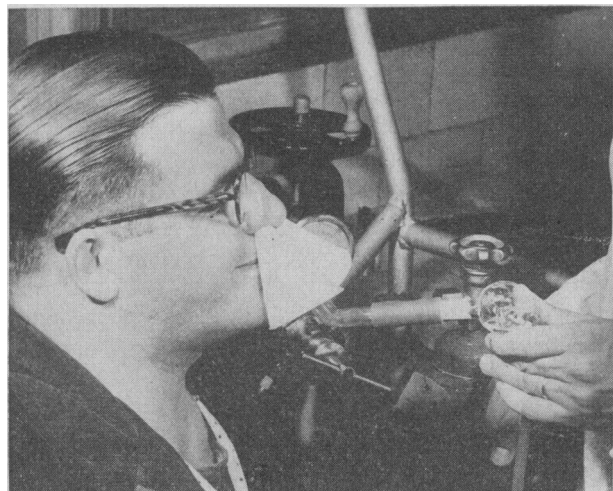


Fig. 1

## OBSERVATION FOR RESPIRATORY DISEASE

Group 1 were closely observed by full-time nurses especially chosen for the task. Every morning, the nurses made a round of all wards in order to detect any case of respiratory disease beginning during the preceding 24 hours. They charted any symptoms and complaints and reported these immediately to the physician. The latter then examined these cases on the same day and made a diagnosis. He recorded the results of his examination on a special card and immediately took a specimen of blood and one of throat washings, which were taken to the laboratory on the same day.

The throat washings were frozen at  $-24^{\circ}$  C.; the material to be used for serological tests was maintained at  $+4^{\circ}$  C.

In groups 2, 3 and 4, persons were observed by physicians who usually looked after them. The physician attached to the service of the establishment was to be consulted at the first sign of respiratory disorder. In practice, contact with the physician was slow and three or four days had already elapsed before the physician was able to make a diagnosis. In other words, necessary specimens could be taken only towards the end of the first week.

Nurses responsible for observation of group 4a investigated at home all absences from school. However, there were very few cases of respiratory disease in this observation group.

## RESULTS

1. *Vaccination Reaction*

Vaccination led to local reaction in 50% of the adults: redness of skin, mild swelling and local

pain. Of those vaccinated, 35% had mild general reactions, such as headaches and chills, which lasted only for a few hours and did not prevent them from following their usual occupations. General reactions of any severity were observed only in 1% of those vaccinated, and kept them at home for a day. We also noticed that the severity of postvaccinal reactions was directly related to the physical activity of the person. Hence manual workers had much more trouble than clerical workers. On the other hand, there were comparatively few reactions in children, and these were of a benign nature. Table II gives a comparison of

TABLE II.—REACTIONS OBSERVED IN CHILDREN AND IN ADULTS AFTER ADMINISTRATION OF INFLUENZA VACCINE

	Number	Reactions				
		None	Slight		Strong	
			Local	General	Local	General
Adults	377	27%	51%	35%	—	1%
Children	190	69%	27%	25%	—	—

reactions seen in two very different groups: factory workers and school children. Among 8000 subjects given the anti-influenza vaccine or the placebo, no allergic reactions were observed.

### 2. Increase in Antibodies after Vaccination

In order to estimate the increase in antibodies arising after vaccination, we relied on the hæmagglutination inhibition and determined specific antibodies in sera coming from the four following groups:

Unvaccinated subjects .....	94
Subjects given placebo solution .....	95
Subjects given one injection only .....	87
Subjects given two injections .....	114

This study showed us that the strain B/Lee/40 used in this experiment was a much more powerful antigen, while on the other hand the strain A/Cuppett/50 had little antigenicity; this is in accordance with the facts shown in Table III.

TABLE III.—MEAN TITRE OF ANTIBODIES FOUND TWO WEEKS AFTER REVACCINATION TWO MONTHS AFTER PRIMARY VACCINATION

Strain	Not vaccinated		Vaccinated— one injection	Vaccinated— two injections
	Number	Placebo	Number	Number
	94	95	87	114
PR 8	1/64	1/93	1/732	1/739
LEE	1/62	1/83	1/520	1/1470
FMI	1/74	1/103	1/226	1/240
Cuppett	1/38	1/56	1/100	1/112

It was also shown (Table IV) that revaccination by the intranasal route had no stimulating or booster effect on the production of antibodies.

TABLE IV.—INFLUENCE OF VACCINATION WITH AEROSOL ON THE ANTIBODY LEVEL. MEAN TITRE IN VACCINATED WITH DIFFERENT VACCINES

Number	Placebo	One injection of vaccine	One injection of vaccine + aerosol two months later
	110	70	90
PR 8	1/59	1/235	1/257
LEE	1/96	1/435	1/435
FMI	1/51	1/133	1/152
Cuppett	1/50	1/105	1/115

### 3. Influence of Age on the Increase of Antibody Titre

Antibody production was found to be independent of the person's age. Persons at the age of 60 responded just as well as young subjects to vaccination with influenza virus A. This is shown in Table V, which compares the antibody titre

TABLE V.—INFLUENCE OF AGE ON THE APPEARANCE OF ANTIBODIES AGAINST THE STRAIN PR 8 AS OBSERVED TWO WEEKS AFTER VACCINATION

Age	Number	Mean titre		
		Before vaccination	After vaccination	Increase of antibodies
15 - 19	17	160	567	x 3.5
20 - 24	9	254	806	x 3.2
25 - 29	23	104	653	x 6.2
30 - 34	22	80	413	x 5.2
35 - 39	12	63	214	x 3.4
40 - 44	20	62	309	x 4.9
45 - 49	23	32	200	x 6.2
50 - 54	30	35	292	x 3.3
55 - 59	14	56	284	x 5.1
60 - 64	17	87	244	x 2.8
Totals	183	68	356	x 5.2

before vaccination with titres found two weeks after the latter.

### INCIDENCE OF RESPIRATORY ILLNESS IN THE VACCINATED GROUP

#### Group 1 (Psychiatric Hospital).

Observation of respiratory disorders was possible only in group 1 (Psychiatric Hospital). Nurses assigned to this task visited the wards and took the temperature of all persons with symptoms associated with illness of the respiratory tract.

Fig. 2 takes into account only patients who had a temperature of 100° F. and more. Nurses took throat washings and early specimens of serum (i.e. during the first day of the illness). Ten days later they took a specimen of convalescence serum. The serum specimens were studied for increase in antibodies corresponding to the various viruses presumed to be responsible for the current infection; an attempt was made to isolate the causative virus from throat washings.

Cases of febrile respiratory illnesses were very rare in November, December and January. In

TABLE VI.—INCIDENCE OF RESPIRATORY ILLNESS DURING THE EPIDEMIC OF INFLUENZA

	One injection of vaccine	Two injections of vaccine	One injection of vaccine, revaccination with aerosol	Placebo	Not vaccinated
1. Mental hospital . . . . .	0.9%	1.1%	1.6%	2.5%	4.6%
2. Civil service, City of Montreal . . . . .	1.4%	—	—	2.5%	5.0%
3. Montreal factory . . . . .	8.3%	—	—	13.7%	—

February there was a recrudescence of respiratory infections, but only in three cases out of 31 were we able to demonstrate the presence of influenza virus. March was more useful as regards the incidence of respiratory illness. In the majority of cases (78 specimens out of 107 investigated) we succeeded in establishing that the infection was influenza. The antigen structure of the influenza virus isolated showed that it belonged to the strain A/Cuppett/50. Interpretation of radiographs taken in 72 persons in whom the influenza virus had been isolated produced only 17 cases of positive pulmonary findings, as follows: pulmonary congestion, 7; bronchitis, 7; pleuropneumonia, 1; lobar pneumonia, 1; unilateral bronchopneumonia, 1.

#### Group 2 (Civil Service, City of Montreal).

In persons belonging to this group we did not succeed in observing respiratory disease so closely. This was not due to the fact that they neglected to mention their symptoms to the physician, but rather that the latter often took two to three days to respond to their call. Thus in many cases symptoms and disease had disappeared by the time the physician arrived. In such cases the physician made a diagnosis of "influenza" on the strength of the patient's statement. Naturally in such cases we were unable to take specimens (blood or throat washings). However, during this period many of the civil servants in the city were absent from work because of respiratory infection (Fig. 3); in fact, during the month of March, when the influenza epidemic was raging, absenteeism for respiratory illness doubled among municipal civil servants.

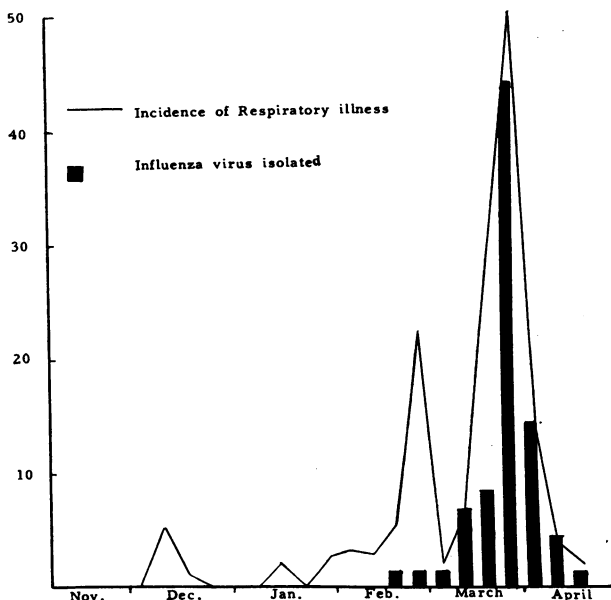
INCIDENCE OF RESPIRATORY ILLNESS AND  
INFLUENZA AS CONTROLLED BY VIRUS ISOLATION  
(Mental Hospital)

Fig. 2

Comparison of the incidence of influenza in various groups shows that it was 0.9%, 1.6% and 1.1% in the three vaccinated groups, 2.5% in the group given placebo solution, and 4.6% in unvaccinated subjects. Hence the protection conferred by influenza vaccine varied between 40 and 80% according to the group. Administration of a booster dose, either by injection or by intranasal vaporization, appears to have added nothing to the protective effect of the first injection of vaccine.

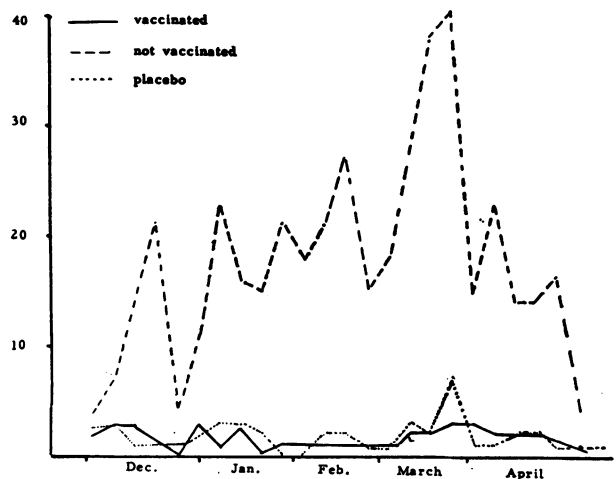
INCIDENCE OF RESPIRATORY ILLNESS  
(Civil Service of the City of Montreal)

Fig. 3

Thus it is logical to conclude that the influenza epidemic had attacked groups 1 and 2 at this time. Moreover, a comparative study of attack rates among the various groups of civil servants reveals a level of protection varying from 40 to 72% in the subjects who were vaccinated.

#### Group 3 (Montreal Factory).

This was the group most affected by respiratory illness. Of those vaccinated in this group 38%

INCIDENCE OF RESPIRATORY ILLNESS  
IN FACTORY M

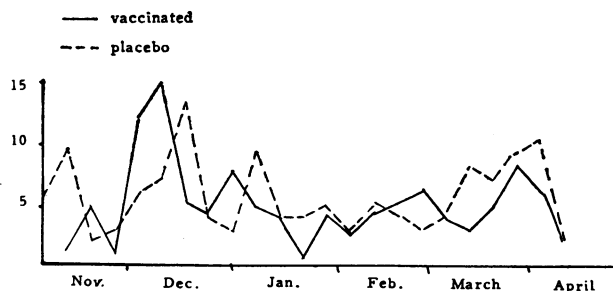


Fig. 4

(120 out of 313) were absent from work because of respiratory illness, against 48% (134 out of 277) of their unvaccinated companions who had been given the placebo.

If we compare the incidence of respiratory illness during March—the time when the influenza epidemic was present in Montreal—we find that 8.3% of the vaccinated persons had a respiratory illness as against 13.7% of the persons given the placebo. Hence vaccination conferred protection of the order of 40% in this case.

#### Group 4 (Montmagny).

There was no respiratory illness in Montmagny in the winter of 1954-55, and the laboratory also appeared to confirm the entire absence of influenza virus from this locality during the relevant period.

#### DISCUSSION

Influenza is a local infection of the respiratory tract. It is characterized by necrotic degeneration of ciliated epithelium which lines the tract.<sup>7</sup> The influenza virus multiplies in the superficial cell layer of the respiratory mucosa.

There is a close parallelism between the subject's resistance to influenza and the titre of antibodies present in the secretions of the respiratory mucosa. It is therefore possible to increase a person's resistance to influenza by increasing this local immunity. Fazekas de St-Groth,<sup>8</sup> working with mice, showed that nasal instillation of anti-influenza vaccine, done either at the same time as or after the intraperitoneal injection of a dose of the same vaccine, made the animal 100 times more resistant to experimental influenza infection. It is also known that penetration into the air channels and fixation on their lining mucosa is better when an aerosol is used than when nasal instillation alone is relied upon. Fixation of droplets present in an aerosol depends on their diameter; the best results have been obtained with particles of size 0.8 to 1 $\mu$ .<sup>9</sup>

Knowledge of these facts led us to administer the second or booster dose of vaccine to the subjects participating in our experiments by nebulization. For this purpose we used the De Vilbiss vaporizer, which produces particles of 1 $\mu$ . diameter.

In our experiments this intranasal nebulization of vaccine did not give the expected results. It gave absolutely no increase in resistance of vaccinated subjects. Zhdanov<sup>10, 11</sup> also noted that intranasal administration of virus inactivated by formol did not increase resistance to influenza infections. On the other hand, he obtained good results by using a living virus.

During the winter of 1954-55 respiratory illness occurred in all the groups observed by us. The attack rate varied from one group to the next. In the factory group out of 313 subjects vaccinated 120 (38%) had respiratory illness, whereas in 277 controls unvaccinated there were 134 illnesses, i.e. 48% (Fig. 2). The municipal civil servants in Montreal had an absence rate of 7.9% and 13% (Fig. 4).

In March there was a recrudescence of respiratory infections in the three Montreal groups under our observation; in fact, it was during this period that we isolated the influenza virus in 70% of cases. In the beginning of the epidemic we isolated it only in 27% of cases, whereas towards the end the percentage of positive results reached 96%. It is possible that this influenza epidemic was preceded in February by an epidemic caused by another virus. Our results are similar to those of Hilleman and his colleagues,<sup>12</sup> who reported that an epidemic of RI-67 infection preceded the influenza epidemic which they studied.

We were entirely satisfied with the antigenic qualities of the vaccine we used. There was an increase in antibody titre against the four component strains. The strain B/Lee/40 proved the most active; the strain A/Cuppert/50 was the weakest.

Using a vaccine of identical composition, Buchner, Reid and Dempster<sup>13</sup> observed a comparable increase in antibodies in vaccinated subjects.

The attack rate for respiratory illness was nevertheless different among subjects receiving the placebo and unvaccinated subjects. At the Hôpital St-Jean-de-Dieu influenza affected 2.5% of the subjects given the placebo, whereas the attack rate was 4.6% for those given nothing. This difference may be explained by the fact that those who received the placebo were in the same wards as the vaccinated. They must therefore have benefited from the protection furnished to the latter. The same explanation holds good for the group made up of civil servants of the City of Montreal. Vaccinated subjects and those given the placebo solution were recruited from among firemen attached to the same fire halls, whereas the control unvaccinated group was composed of men belonging to other fire halls. In this group we also arrived at the conclusion that vaccinated and less affected subjects protected to a certain extent their placebo-inoculated companions; in fact, there was 50% less respiratory illness among them than among firemen from other fire halls.

## SUMMARY

During the winter of 1954-55 we attempted to evaluate in human subjects the effectiveness of a quadrivalent anti-influenza vaccine.

An epidemic of mild influenza affected Montreal in March 1955, and its origin was traced to a virus of antigenic structure identical with that of virus A/Cuppett/50.

The quadrivalent vaccine given in our study led to an appreciable production of antibodies; their titre was quadrupled for strains A/PR8/34 and B/Lee/40, the response being much weaker with strains A/FMI/47 and A/Cuppett/50.

This quadrivalent vaccine conferred a protection against clinical influenza varying between 40% and 80% according to the group.

Our thanks are due to Dr. G. Charette, epidemiologist of the City of Montreal, and Dr. A. Dumas, director of the Montmagny Health Unit, for their help in this study.

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SUBARACHNOID HÆMORRHAGE,  
1951-1958: 108 Cases\*

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OUR FIRM CONVICTION of the practical inefficacy of emergency operation for subarachnoid hæmorrhage was the reason which dictated our method of treatment.

As our treatment has been systematically the same for all patients in this group, we think that the present analysis may be of value in showing whether our final results can be compared with those from other methods of treatment, and whether this treatment has been better or worse for our patients.

\*From the Neurological and Neurosurgical Services, Hôpital de l'Enfant-Jésus, Québec.  
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## RÉSUMÉ

Au cours de l'hiver 1954-1955 nous avons tenté d'évaluer chez l'homme l'efficacité d'un vaccin quadrivalent.

Le vaccin a été préparé à l'Institut de Microbiologie et d'Hygiène de l'Université de Montréal à partir des souches suivantes: A/PR8/1934, B/Lee/1940, A/FMI/1947 et A/Cuppett/1950. La vaccination a été faite 1) à l'Hôpital pour les maladies mentales, 2) dans le service civil de la ville de Montréal, 3) dans une usine de Montréal et 4) dans une localité semi-rurale sise 40 milles en aval de Québec. Dans tous ces groupes les sujets ont été divisés dans les sous-groupes suivants: 1er sous-groupe ayant reçu une injection de vaccin, 2e ayant reçu deux injections de vaccin, 3e ayant reçu une injection de vaccin avec la vaccination de rappel par aérosol, 4e ayant reçu une injection de placebo. Dans le groupe 1 et 2 nous avons observé aussi des sujets non vaccinés qui habitaient dans les mêmes conditions que les sujets vaccinés. Au total 5494 sujets ont reçu le vaccin antigrippal, 2254 ont reçu une injection de placebo et 3543 ont servi comme témoins non vaccinés.

Le vaccin quadrivalent employé en cette circonstance donna lieu à une production d'anticorps appréciable, leur taux quadruplé pour les souches A/PR8/1934 et B/Lee/1940, la réponse restant beaucoup plus faible avec les souches A/FMI/1947 et A/Cuppett/1950.

Une épidémie de grippe bénigne a sévi à Montréal en mars 1955 et on a pu en relier l'étiologie à un virus de structure antigénique identique au virus A/Cuppett/1950.

En comparant la fréquence de la grippe chez les sujets en observation à l'hôpital des maladies mentales on remarque qu'elle a été de 0.9%, 1.1% et 1.6% dans les trois sous-groupes de vaccinés, de 2.5% dans le groupe ayant reçu la solution placebo et de 4.6% chez les sujets non vaccinés.

Dans le deuxième groupe (Service civil de la ville de Montréal) nous avons observé que 1.4% des vaccinés, 2.5% des sujets ayant reçu une injection de placebo et 5% des témoins non vaccinés se sont absentes de leur travail à cause des maladies respiratoires.

Dans l'usine M., où le taux des maladies respiratoires a été très élevé, pendant l'épidémie de la grippe nous avons observé 8.3% des maladies respiratoires parmi les vaccinés et 13.7% parmi ceux ayant reçu le placebo.

Ces résultats permettent de conclure que le vaccin quadrivalent donna contre l'influenza clinique une protection variant de 40 à 80% selon les groupes.

## TREATMENT

1. No intracranial operation is performed before at least 15 days after the hæmorrhage. Angioma and intracerebral hæmatoma are the only indications for such operation.

2. On admission, whatever his condition, the patient is put on a "uniform medical" treatment until his physical and neurological conditions have improved sufficiently to allow arteriography to be done with fair security.

3. A lumbar puncture, if indicated, is performed on admission, and only a few drops of fluid are withdrawn — enough to confirm the diagnosis.

4. The most absolute rest is imposed. The least physical efforts are avoided by the patient, who is fed for at least one week with adequate feedings and fluids. As soon as possible the exact problem is explained to the patient; the purpose of our treatment is also explained to him in order to obtain his full co-operation and to reduce his anxiety.