

The pathology of these cases is not fully understood; they are attributed to perineural oedema of the affected roots or nerves, comparable to the urticaria of serum sickness. Hughes (1944) has suggested, without any direct evidence, that they are due to a virus infection, the organism being introduced at the injection of the serum.

There is complete clinical similarity between the serum cases and the type of case described in this paper, and it is reasonable to assume that they are of similar aetiology.

There were no deaths in our series, and, in view of the recovery to be expected, biopsies of affected nerves were considered unjustifiable. It is doubtful if any comparable condition occurs in the lower limb; isolated external popliteal-nerve lesions are common, but many of these are pressure palsies, and in the cases where there is no evidence of pressure there has rarely been any pain.

NOMENCLATURE

None of the names applied to this condition are satisfactory, and most of them are inaccurate: infective neuritis, localised neuritis of the shoulder girdle, and acute brachial radiculitis all imply an infective origin, which is uncertain, and suggest that the disease is limited to either peripheral nerves or nerve-roots. A more general name seems preferable, and we suggest that until the pathology and aetiology are known it should be called "neuralgic amyotrophy."

SUMMARY

A syndrome consisting in severe pain across the shoulder and upper arm, followed by atrophic paralysis of muscles round the shoulder girdle, is described.

On clinical grounds it is thought that the pathological process can involve one or more peripheral nerves, two or more spinal roots, or the spinal cord.

The condition appears to be a distinct clinical entity which became increasingly common during the war years.

A similar syndrome may occur some days after the injection of serum, and the two conditions are probably identical, though the aetiology is unknown.

The name "neuralgic amyotrophy" is suggested.

Our thanks are due to the late Dr. George Riddoch, to Dr. Hugh Garland, and to Dr. P. S. Buckley, with whom we often discussed the condition, and to the many medical officers who referred cases to us.

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VACCINATION AGAINST INFLUENZA A

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MANY attempts to use formolised virus vaccines for protective inoculation against influenza have been made since the first trials in 1937 with virus contained in mouse-lung filtrates (Stuart-Harris et al. 1938). The possibility of using much more potent preparations arose from the discovery of Nigg and her colleagues (1940) and Burnet (1941) that virus could be obtained in very high titre in the allantoic fluids of infected eggs. Later Francis and Salk (1942) described a method of concentrating and purifying such vaccines by adsorption on, and elution from, chicken red cells; and Stanley (1944) and his co-workers developed a method of achieving the same end by differential centrifugation.

Vaccines thus improved have been used very extensively in the American Army. Controlled trials with concentrated vaccine (mixed A and B) have given very encouraging results in the U.S.A. Thus, against influenza A in 1943 (Commission on Influenza, 1944) a reduction in incidence to about a fourth was achieved in five of six centres; at the sixth, in California (cf. Eaton and Meiklejohn 1945), the reduction was doubtfully significant. Even better protection against influenza B is suggested by the reports of Francis et al. (1946) and Hirst et al. (1947); the incidence of influenza B in inoculees was 11% and 5% of that in uninoculated groups. Hitherto, trials in this country have been unsatisfactory because, in the communities under observation, an influenza outbreak with a high incidence has not appeared within a reasonable time. In two groups under observation in 1946, however (Dudgeon et al. 1946), an apparent reduction in incidence of influenza B to a fifth and a half was achieved by vaccination. These groups were the only ones with a fairly high incidence of infection; in other groups, with a low incidence, little if any benefit from inoculation was demonstrable.

PLAN OF INVESTIGATION

An attempt was made during the winter of 1946-47 to test further the value of influenza vaccination in Britain. The vaccine used was made from infected allantoic fluids inactivated with 1:2000 formalin and concentrated by Francis and Salk's (1942) method.

Most of that used was made by the Commonwealth Serum Laboratories, Melbourne (virus A, Melbourne strain), but some was prepared by the South African Institute for Medical Research, Johannesburg (A, P.R.8 strain), and some by the Connaught Laboratories, Toronto (P.R.8 strain). Though the vaccines had been kept in the cold (-1°C) for over a year, all batches were still potent as judged by Salk's modification of the Hirst test, fowl red cells being usually agglutinated to a titre of 1:2048. All of that used in the Army and school trials was made from Melbourne virus.

The vaccine was tested by measuring the antibody response to a subcutaneous injection of 1 ml. in 46 adult volunteers; these people were bled at the time of vaccination and again two weeks later. The rise in antibodies was measured by means of Salk's modification (1944) of Hirst's test, and using an antigen made from the P.R.8 strain of virus. The results are shown in fig. 1. If a fourfold rise in antibodies is taken as a positive result, 38 persons (83%) gave a positive response to the injection; the average rise was over sixfold. In 6 of the 8 negative results the original antibody level was fairly high; it has been previously observed by

other workers that under these conditions there is often no further rise as a response to injection or to a clinical attack of the disease. From the above results we concluded that the vaccine was suitable for a clinical trial.

SCOPE OF THE TRIAL

Epidemiologists are familiar with the idea that vaccination of part of a community may, by reducing chances of spread of infection, lead to a lowered incidence of disease even in the unvaccinated members of the group. Salk and colleagues (1945) have emphasised the likelihood of such a phenomenon in the case of influenza. In previous trials of vaccines we have used the strict alternate-case method to obtain controlled results. In the present investigation some trials were made in this way; in other trials whole groups were, so far as possible, vaccinated, and results in them contrasted with those in comparable uninoculated groups. We thus hoped to learn something of the liability to influenza of an immunised herd as well as that of an immunised individual. In nearly all our groups, however, the inoculated groups were able to mix with control groups during part of the day—during school-hours in the case of school-boys, in canteens in the case of Army recruits.

Prophylactic vaccination was carried out under controlled conditions during November and December, 1946, in 24 mental hospitals, 3 public schools, and numerous smaller communities, including 2 preparatory schools, nursing staffs of hospitals, and some patients of general practitioners. In 18 Army training centres alternate intakes were vaccinated, starting at some centres in November, 1946, and at others as late as Jan. 2, 1947. Altogether some 20,000 people were inoculated, there being about an equal number of uninoculated controls living under similar conditions. Unpleasant reactions to the inoculations, both general and local, were satisfactorily few.

INCIDENCE OF THE DISEASE

Conclusive results from all these sources were disappointingly small for several reasons, the most important being the mild clinical picture and the low incidence of the disease. Many cases of true influenza were undoubtedly missed in the Army, and probably a smaller number in the mental hospitals. A complete serological check of all controls either by hæmagglutination methods or complement-fixation tests would have been the only way to estimate the incidence more accurately, and this was not practicable. A considerable number of complement-fixation tests were done by Dr. A. J. H. Tomlinson, of the Central Public Health Laboratory, Colindale, on

samples of late convalescent serum from Army recruits known to have experienced an influenza-like disease early in 1947. These results provided laboratory evidence of the presence of influenza A in the units concerned.

The disease was mild and did not show its usual facility for rapid spread except in a few epidemics among school-children and in prisoner-of-war camps and Army training centres. The highest attack-rate in any Army training centre using the vaccine was 14.5% of controls; in one boys' school it was 22% of controls; but in seven mental hospitals only sporadic cases were reported and serologically confirmed. The experience of general practitioners interested in influenza leads us to suppose that the incidence in mental hospitals was not very dissimilar from that among the same age-groups in the general population. The incidence of influenza was so low among the smaller communities, such as the hospital nursing-staffs, that the results were not worth considering.

INFLUENZA IN BOARDING-SCHOOLS

Almost the only communities, apart from prisoner-of-war camps, to experience real epidemics were schools in the southern half of England. Epidemics occurred in two of the three boarding-schools using the vaccine, and through the kindness of Dr. W. H. Bradley, of the Ministry of Health, other schools were visited while epidemics were in progress.

The clinical picture of influenza in the winter of 1946-47 is best illustrated by some of the unvaccinated schools.

On Jan. 21 a girls' boarding-school was visited near the height of its epidemic. The 13 recently admitted patients all complained of headache, stuffy nose, sore throat, malaise, shivering, and a dry cough. Their temperatures averaged 102.5°F and pulse-rates 120 per min.; all had red injected throats, with, in some, hypertrophied lymph-nodes on the posterior pharyngeal wall. The course of the disease was typically short; the temperature remained high for only 24-36 hours, after which it fell rapidly to normal; but it sometimes rose to a second, smaller, spike one or two days later. Five days after the onset of symptoms most children were perfectly well. Influenza virus A was grown in fertile eggs from garglings taken on Jan. 21, and complement-fixation tests done on 8 convalescent sera all showed high (1:32 or 1:64) titres against influenza virus A (P.R.8). The over-all attack-rate in this school was 34%; it was a clear-cut epidemic uncomplicated by any other disease.

On Jan. 24 the onset of a clinically similar epidemic was seen in a large boys' school. The symptoms were identical, but the attack-rate—21%—was lower. Here also influenza virus A was grown from garglings, and blood samples gave positive Hirst test results. An attack-rate of 70% was encountered by Dr. A. M. MacFarlan in a school of 250 boys which he was investigating.

The largest vaccinated school to experience an epidemic consisted of 614 boys, of whom just over 400 were in one large house with eleven dormitories, and about 60 in each of three smaller, separate, houses. The dormitories contained all ages from 13 to 18 years. In the day-time the boys mingled for classes, meals, and games. In the large house alternate dormitories had been vaccinated, and in the smaller houses 2 out of 3 were inoculated as completely as possible on Dec. 12 and 13, 1946; it was impossible to vaccinate all the boys, since some parents refused permission. Altogether there were 305 vaccinated boys and 309 controls. The original intention was to compare the subsequent incidence of influenza in (1) immunised and unimmunised boys (alternate cases), and (2) immunised and unimmunised groups of boys (alternate groups). The school reassembled on Jan. 25 for the spring term. Next day 2 boys were admitted to the sanatorium with a diagnosis of influenza, and this was the beginning of an epidemic which reached

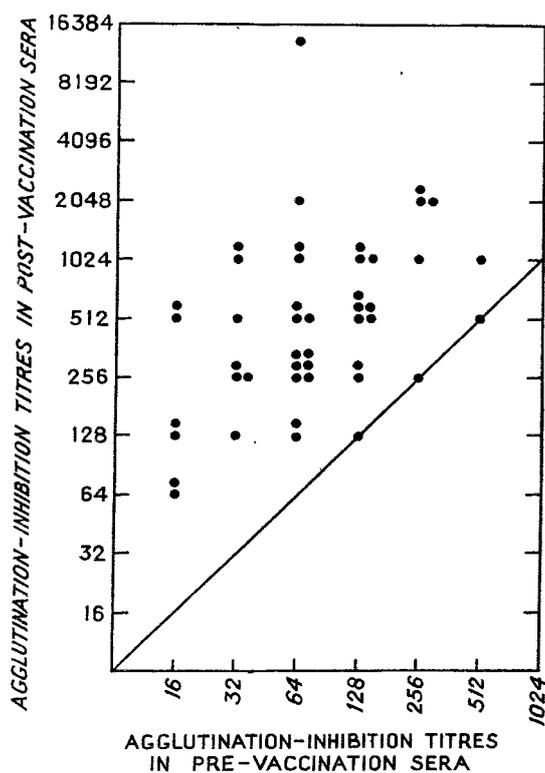


Fig. 1—Influenza-A antibody-response to vaccination in 46 persons.

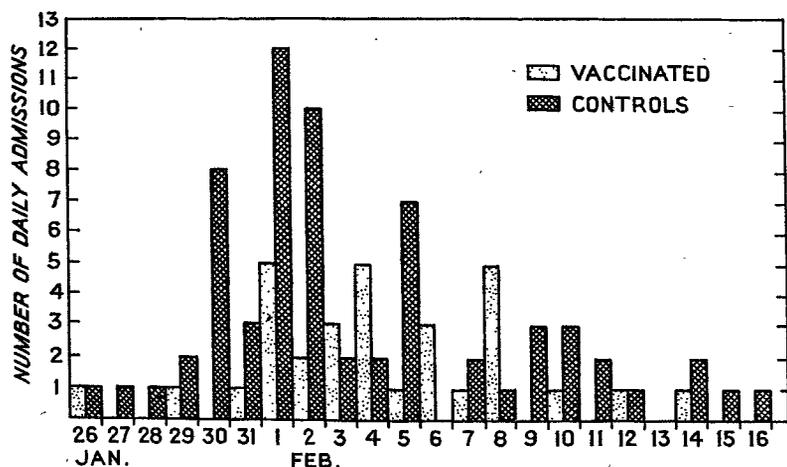


Fig. 2—Incidence of influenza and feverish colds during the spring term, 1947, in a school of 612 boys, of whom 305 had been vaccinated.

its peak on Feb. 2. Influenza virus A was again successfully grown in eggs. The clinical picture of this epidemic was not nearly so uniform as in the unvaccinated schools, about a third of the patients having no more than slight feverish colds with a temperature below 100°F; in the absence of an epidemic, these cases would not have been diagnosed as influenza. Fig. 2 shows the daily admissions of vaccinated and control boys for all cases, varying from slight feverish colds to typical influenza.

From this it can be seen that, during the epidemics, febrile upper respiratory infection was twice as common in the controls as in the vaccinated; when an attempt was made to count only those boys with typical influenza, the comparative incidence in the two groups seemed to be the same. The clinical attack-rate for all febrile upper respiratory infections was 22% among controls and 11% among the vaccinated. The curve of increased upper respiratory infections coincided with that of typical influenza; so probably most of the "feverish colds" were, in fact, mild influenza. Fig. 2 shows that initially the incidence of disease was much higher among the controls, but that after some days more cases occurred among the vaccinated; so the final advantage to the vaccinated was not very great.

Among boys in the control (uninoculated) dormitories and houses the attack-rate was 21.5%, or almost exactly the same as the rate among all uninoculated boys in the school (21%); the uninoculated boys living in separate houses did not appear any more susceptible to influenza than the total controls.

A complicating factor in this school was a coincident measles epidemic. Some of the boys in the prodromal stage of measles were at the same time harbouring the influenza virus, as was proved by recovering the virus from garglings in boys who three or four days later produced a typical measles rash. Any boy having prodromal symptoms for longer than five days, or who had a separate febrile upper respiratory infection later followed by a typical prodromal measles fever, was counted as having had influenza or a feverish cold for the purposes of this investigation. We could not investigate each case by taking garglings for cultivation in eggs. We did, however, obtain laboratory evidence from garglings that some of the mild cases in vaccinated boys were genuine influenza. We also had serological evidence that some of the controls had a very mild attack with a temperature of no more than 100°F.

The second partly inoculated school to experience an epidemic was one of 327 boys. Here more than half (206) had been vaccinated in December, 1946, in response to an unexpectedly high volunteer-rate among parents. The school reassembled on Jan. 17; and on Jan. 21 there were 2 cases of influenza. A small epidemic followed involving 23 (11%) of the vaccinated boys and 21 (17.3%) of the controls. These were in boys admitted to the sanatorium; there were also some very mild

feverish colds among boys treated in their "houses" and of whom no records were kept. For the rest of the term there were sporadic cases of an influenza-like disease, and of streptococcal tonsillitis, besides a few cases of measles.

There is little to suggest that the vaccine accounted for the mild type of disease in these schools, since many mild cases are known to have occurred in the Army; moreover, a rather similar state of affairs was seen in some other schools where no vaccine was used.

RESULTS IN THE ARMY

Between November, 1946, and February, 1947, the influenza vaccine was used in 18 Army training centres. These were chosen because the incidence of influenza is usually much higher in recruits than in seasoned troops. Alternate fortnightly intakes of recruits were vaccinated, beginning in some places with the intake of Nov. 22, 1946. Intakes varied in size between 100 and 450 men. Those in primary training centres remained in the barracks for 6 weeks of training before being posted elsewhere, and the others for 10–12 weeks. In all, 5000 inoculations were done and 4000 uninoculated men acted as controls. It was planned that medical officers should keep dated records of all upper respiratory infections among the men, both controls and vaccinated. No training centre had any epidemic of major proportions, but there was certainly a minor prevalence of mild influenza in many units in January and February, 1947. Assessment of results was difficult because influenza in 1947 was extremely mild and the distinction of influenza from other respiratory infections correspondingly difficult. Since this diagnosis was made by many different medical officers, there was obviously considerable variation in what was labelled clinical influenza and what was regarded as a cold or febrile catarrh. The success of these vaccination trials in the Army training centres depended on the presence of an easily recognisable clinical entity, true to type and affecting many units; this was unfortunately lacking. At several centres there were undoubted cases of influenza, later confirmed by serological tests; but only three units experienced definite outbreaks subsequent to vaccination.

In one of these centres (a training brigade of Royal Engineers at Cove, Aldershot) an outbreak in the second week of January, 1947, affected 15 of 101 uninoculated men of the Dec. 5 intake (see fig. 3). It did not spread to men of the next (Dec. 18) intake, though these were not inoculated until the outbreak was in full swing; but complement-fixation tests raised grave doubts about whether the outbreak was influenza or not.

In an Army training centre at Richmond, Yorkshire, there was little evidence of influenza among the intakes of Dec. 5 and Jan. 1. In the next intake, that of Jan. 16, which was an uninoculated group, 27 cases occurred among 186 men. Unfortunately the next, vaccinated, intake (Feb. 6) had 19 cases among 190 men. At Shrewsbury, in another Army training centre, influenza hit the middle two of four intakes: that of Jan. 16 (uninoculated) had 12 cases in 105 men, while that of Feb. 6 (vaccinated) had 15 in 106 men. Complement-fixation tests on convalescent sera from Richmond and Shrewsbury mostly showed high (over 1:32) titres; so probably these centres experienced true influenza outbreaks. Taking together the results from the two centres, the incidence of clinical influenza was, in 619 vaccinated men 7.1%, and in 651 controls 8.3%. Fig. 3 includes also for comparison results obtained in units at Canterbury and Cardiff. As will be noted, the trend of the results is much the same as elsewhere, but no detailed analysis was thought to be worth while, since numbers were considerably smaller.

It can be argued that no favourable result could be expected from vaccination after the beginning of

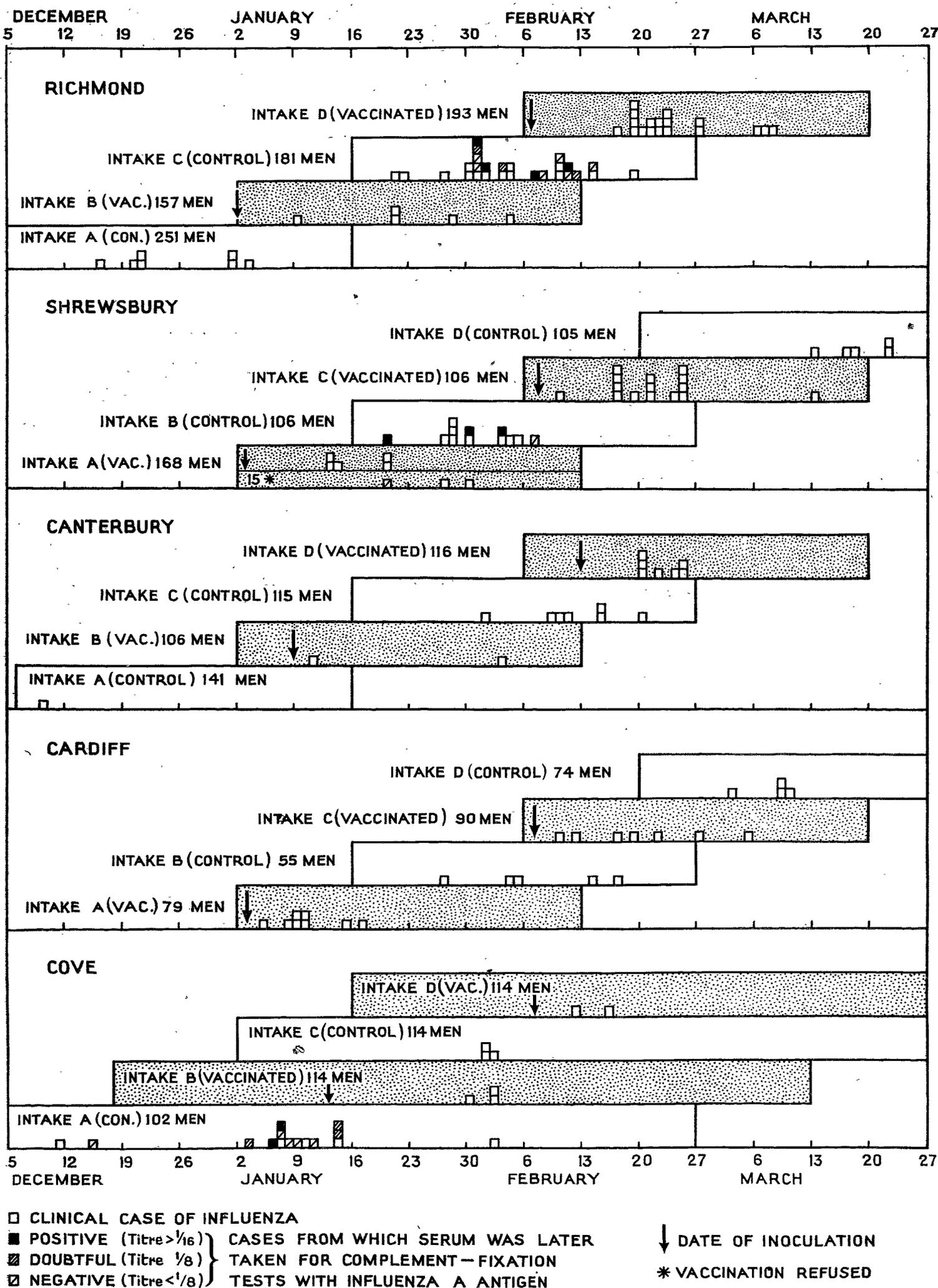


Fig. 3—Influenza at five Army training centres in the winter of 1946-47.

February, for by then the influenza wave in the country as a whole had passed its peak. Quite certainly, however, we could have obtained an apparently favourable but wholly fallacious result by excluding from consideration all the intakes of Feb. 2 and onwards; for among two vaccinated groups entering about that time the incidence was much the same as that among control groups entering in mid-January.

INFLUENZA IN MENTAL HOSPITALS

Of the 24 mental hospitals which used the vaccine, only 7 reported any cases of influenza; these were sporadic and far too few to help in assessing the effect of vaccination. Since in several instances the presence of the virus was confirmed either by cultivation in eggs or serologically among one or two patients in a ward, it is surprising that the disease did not spread.

The largest number of cases was that reported from a mental hospital in Surrey. Here among 1000 patients taking part in the investigation 32 cases of influenza were diagnosed clinically as having influenza; of these, 20 were among the 500 controls and 12 among 500 vaccinated persons. Serological evidence of infection with influenza virus A (Hirst test) was found in 8 out of 14 blood samples from controls; the virus was isolated from 1 vaccinated patient. The materials were kindly sent to us by Dr. G. A. Lilly.

DISCUSSION AND SUMMARY

In the autumn and winter of 1946-47 a formalised influenza-A vaccine was given to about 20,000 people; about an equal number living under the same conditions were designated as uninoculated controls.

In twenty-four mental hospitals and some small groups the incidence of influenza was so low that no conclusions about the efficacy of the vaccine could be drawn.

In two out of three schools in the trial there were outbreaks of influenza. In one the incidence in the vaccinated boys was 11% and in the controls 21%; in the second the incidence was 11% in the vaccinated, and 17.3% in the controls. The results in this second school were somewhat obscured by concurrent streptococcal tonsillitis.

In only three of eighteen Army training centres under study did an outbreak of upper respiratory disease take place after completion of the inoculations; and one of these was very doubtfully influenzal. In the other two the incidence of influenza was 7.1% in the vaccinated and 8.3% in the controls—not a significant difference. The only safe conclusion is that, in the absence of a widespread epidemic involving many units under observation, a trial on the lines described is unlikely to give a definite answer.

Our results show that, even in communities apparently favourable for vaccination, present-day vaccines have not produced any striking reduction in incidence. No conclusion can be drawn from this study about the merits of attempting to immunise whole communities, theoretically reasonable though this may be.

The results are much less encouraging than those reported in 1944 and 1946 from the United States; on the other hand, recent reports from there (Francis et al. 1947, Sigel et al. 1947) indicate that in 1947 vaccination had little, if any, effect on the incidence of influenza. Apparently the strains of virus A causing the 1947 epidemics were antigenically rather remote from those contained in the vaccine. Further studies, especially of antigenic relations among strains of influenza viruses, are necessary before general use of influenza vaccines can be advocated.

We wish to acknowledge the willing help of many medical officers in the Army: at schools, and at mental homes and

hospitals, and in particular Dr. W. H. Bradley and Dr. G. E. Godber, of the Ministry of Health; Brigadier E. A. Richmond, director of hygiene, War Office; Dr. G. F. Hawkins and Dr. C. H. Harley; and Dr. Robert Cruickshank and Dr. F. O. MacCallum, of the Central Public Health Laboratory, Colindale.

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PRIMARY PULMONARY COCCIDIOIDOMYCOSIS

CASE OF LABORATORY INFECTION IN ENGLAND

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THE occurrence of a case of primary pulmonary coccidioidomycosis in England is a medical curiosity, but in view of the dangers of laboratory infection it is considered that this case should be recorded.

Human infection with the organism *Coccidioides immitis* was first recorded at the end of the nineteenth century in South America and California in the form of a chronic and often fatal granuloma affecting the bones and other tissues. This was the only form of the disease recognised until Gifford (1935) and Dickson (1937) drew attention to the fact that, in the parts of California from which the patients with coccidioid granulomata usually came, there was another endemic disease called San Joaquin Valley fever or "the bumps." This condition is characterised by an acute febrile respiratory infection associated with erythema nodosum, and by skin tests and sputum examination it was shown that this disease represented a primary pulmonary infection with the organism, which usually cleared, conferring immunity on the patient, and only very rarely went on to hæmatogenous dissemination and granuloma formation. These investigators also showed that many cases of respiratory infection without erythema nodosum were due to the same organism.

Our knowledge of the primary infection has been greatly increased during the recent war because, owing to the suitability of the climate in the affected areas for flying training and military exercises, many American servicemen lived in or passed through them. Skin-test investigations reported by Lee (1944) and Smith et al. (1946a) have indicated that subclinical infections are four times as common as clinical cases, and that the prognosis is good, dissemination occurring in 1 in 380 infections in white races, though the figure for negroes is 1 in 30.

The organism, when found in lesions in the body, appears as a spherule which produces endospores which in turn give rise to fresh spherules. If the endospores are expelled from the body they develop a mycelium and chlamydospores; this form is seen on culture and when the organism is growing on the ground in endemic areas. The chlamydospores are the source of fresh human infections, which are therefore more common when the chlamydospores are blown about in dry weather (Smith et al. 1946b).