J. Hyg., Camb. (1967), **65**, 485
Printed in Great Britain

An assessment of oil adjuvant and aqueous influenza vaccines

I. Reactions to the vaccines*

BY J. R. L. FORSYTH†
Department of Microbiology, The Queen's University of Belfast, Northern Ireland

(*Received* 19 *May* 1967)

INTRODUCTION

During the earliest trials of influenza vaccines (Francis & Magill, 1935–6, 1937) reactions to the inoculum were noticed. Hirst, Rickard & Friedewald (1944) found that about 1 in 200 of those inoculated with 1·0 ml. of formalized vaccine developed a fever of more than 100° F. and that moderately sore arms were common. Norwood & Sachs (1947) noted that 77·3% of a group of industrial workers suffered from sore arms after vaccination and 29·5% of them became febrile. Salk (1948) showed that reactions were associated with the virus content of the vaccine and not with the presence of impurities. Griffin (1959) found that the proportion of U.S. Army personnel requiring treatment after influenza vaccination fell from 11·33/1000 in 1953 to 2·83/1000 in 1955 and in view of the large numbers of inoculations given this might have reflected an improvement in the vaccine. In Britain, Cope (1960) inoculated over 3000 people and reported 'about half a dozen' were absent from work as a result. Early trials using oil adjuvant vaccines (Henle & Henle, 1945) were marred by the high incidence of local reactions yielding residual sterile abcesses, and Beebe, Simon & Vivona (1964) showed that cysts occurred in 3% of subjects in large-scale trials of 1951–3 although an improved technique of inoculation was used. However, using a purified emulsifying agent, Himmelweit (1960) found none of these reactions in his group of 160 volunteers.

Although it seemed from these recent trials that both the aqueous and oil adjuvant vaccines were now relatively innocuous, Clarke (1962) and also Meichen, Rogan & Howell (1962) reported that contemporary commercial aqueous influenza vaccines were causing an undesirable number of reactions. Because of these conflicting reports, trials were carried out to assay reactions to various types and doses of influenza vaccines and this paper describes the results.

* This material was included in a thesis submitted to the University of Capetown in partial fulfilment of the requirements for the degree of Doctor of Medicine.

† Present address: Department of Microbiology, Monash University Medical School, Prahran, Victoria 3181, Australia.

MATERIALS AND METHODS

Trials

Two trials were carried out, the first over the winter of 1962–3 and the second in 1963–4.

First trial

In the first trial there were two parts. In both parts the volunteers were first to fifth-year medical students at the Queen's University of Belfast. In the first part, which began in November 1962, all volunteers whose date of birth was an odd number (e.g. 1st, 3rd, etc. of the month) were given aqueous vaccine, and those with even-numbered birthdays received placebo. The second part started in January 1963, in such a way that there were 8 weeks between inoculations. The same group of volunteers took part, with a few changes detailed below, and now all those with birthdays in the first half of a month were given an adjuvant vaccine, and those born in the second half of a month received aqueous vaccine.

In each part inoculation was carried out in the morning and the volunteers were examined on the same afternoon, and thereafter on the 1st, 2nd, 3rd and 7th days, and finally 21 days after the first inoculation and 28 days after the second. Blood samples for antibody studies were taken at the time of inoculation and at each last examination.

At every examination each volunteer's card was marked with the degree (0–3) of local or general reactions found. The card bore columns for erythema, pain, tenderness, lymphadenitis, malaise, fever, generalized aches and pains, nausea or vomiting, diarrhoea or constipation, headache, coryza, allergic manifestations and other signs and symptoms. Neither the volunteers nor the examiners were aware of which inoculum had been given until after the trial.

Second trial

In the second trial the volunteers were first-year medical students of the Queen's University or nurses from the Royal Victoria and Royal Maternity Hospitals, Belfast. All these volunteers were given a new adjuvant vaccine and were examined 2, 7, 28 and 90 days after inoculations. The same manifestations were sought as in the first trial, but the layout of the cards was modified and improved. Owing to the absence of a control group, the information can only be regarded as supplementing that from the first trial. Blood samples were taken at inoculation and at 28 and 90 days afterwards.

Vaccines

The first inoculations of the 1962–3 trial were 0·5 ml. volumes of either placebo (phosphate-buffered saline) or aqueous vaccine (*Invirin*, Glaxo). These were administered subcutaneously over the triceps. In the second part of the trial either 1·0 ml. *Invirin*, subcutaneously, or 0·25 ml. oil adjuvant vaccine, into the belly of the triceps, was given. In the second trial the new, augmented, adjuvant vaccine (*Admune*, Evans Medical) was inoculated into the upper part of the long head of the triceps.

Analysis

In this paper statistical significance was assessed using the χ^2 test without Yates's correction and significance was read when $P \leqslant 0{\cdot}05$. Where the expected number was too small to use χ^2, an exact probability was calculated.

Table 1. *The nature of inocula used in the trials, with their antigenic content in haemagglutinating units (HAU).*

	Trial 1962–3				
	First part		Second part		Trial 1963–4
Strains of influenza virus	Placebo	*Invirin* (aqueous vaccine)	*Invirin* (aqueous vaccine)	Adjuvant vaccine	*Admune* (adjuvant vaccine)
A/Singapore/1/57	—	3750*	7500	1500	1500
A/England/1/61	—	1250	2500	500	500
B/England/939/59	—	2500	5000	1000	1000
B/Taiwan/4/62	—	—	—	—	500
	Phosphate buffered saline 0·5 ml.	In 0·5 ml. dose	In 1·0 ml. dose	Per 0·25 ml. dose	Per 0·25 ml. dose

* Haemagglutinating units.

RESULTS

First trial, part 1 (*November–December* 1962)

Three hundred and eighty volunteers took part, but only 281 were examined on every occasion and yielded complete records. The remainder missed one or more sessions. Absenteeism was apparently not governed by the vaccine received ($0{\cdot}3 > P > 0{\cdot}2$), but was associated with the inconvenience of attending for examination. The results of those who had incomplete records were not markedly different from those with complete records. The figures supplied refer to the records of all volunteers.

Local reactions

The principal local reactions were erythema, pain and tenderness.

Erythema around the site was scored from 0 to 3. An area up to 15 mm. in diameter was indicated by '1', more than 15 mm. by '2', and widespread erythema by '3'.

Pain was assessed by asking volunteers whether their arms hurt or hindered them and was scored '0', '½' (minimal), '1' (slight), '2' (moderate) and '3' (severe). Minimal pain amounted to awareness of having been inoculated.

Tenderness was elicited by the response to questioning and firm palpation of the inoculated area. It was graded in the same way as pain.

Compared with the placebo injection of 0·5 ml. of saline, the same volume of *Invirin* produced reactions significantly more often. Erythema only occurred after

https://doi.org/10.1017/S0022172400046027 Published online by Cambridge University Press

the vaccine and there were more reports of tenderness from those who were given vaccine at each examination for the first 3 days ($0{\cdot}05 > P > 0{\cdot}025$ some hours after inoculation, $P < 0{\cdot}0005$ on days 1–3). However, a few hours after the inoculation 'pain', as defined above, appeared to be a function of the injection process itself because it was only on the second examination that the vaccinated group yielded more complaints, ($0{\cdot}01 > P > 0{\cdot}005$).

Table 2. *The incidence of the main local reactions associated with the first trial, part 1*

Reaction		Placebo 0·5 ml., 186* (%)	*Invirin* 0·5 ml., 194* (%)
Erythema	0	100·0	68·5
	1	0	13·5
	0	0	17·6
Pain	0	81·8	72·4
	½	7·5	13·5
	1	10·2	12·4
	2	0·5	1·7
Tenderness	0	93·0	58·5
	½	3·2	20·7
	1	3·2	19·2
	2	0·6	1·6

* Number of volunteers.

Although induration and swelling of the inoculated arm only occurred in those who received vaccine the incidence was small, the greatest on any day being 6/175. An attempt to use the measurement of arms as an index of reaction had to be abandoned as swelling was so inconspicuous. Both types of inoculation caused bruising at the site in a proportion of cases, but rather more bruises followed vaccine. The greatest number was seen on the third day when 10·3 % of the vaccinated group and 6·0 % of those with placebo had bruises.

Systemic reactions

There was no evidence that this small dose of vaccine caused systemic reactions. In the first 3 days after the inoculation, coryza, influenzal symptoms and malaise were more common among those given placebo (coryza in 3·8 % against 1·5 %). Two cases of migraine and one of paroxysmal tachycardia during the week after inoculation occurred in students given placebo.

No allergic manifestations occurred before 3 days after inoculation. After this, one case of a transient maculo-papular rash and one of localized urticaria occurred in students who had been given vaccine and a more pronounced urticaria in one of those given placebo.

General responses

On the seventh day, each volunteer was asked whether the inoculation had interfered with work, play or social activities. Five complaints were received, three from volunteers who had received placebo and two from those given vaccine.

First trial, part 2 (January–February 1963)

Three hundred and forty-two volunteers took part in this phase, and 267 were examined on all occasions. Three extra volunteers who had received no vaccine before joined the trial; 26 of the placebo group and 15 who had had vaccine left the trial. The reactions of those who left had been no more severe than the average.

Table 3. *The incidence of the main local reactions associated with the first trial, part 2*

Reaction		Adjuvant vaccine, 158* (%)	*Invirin* 184* (%)
Erythema	0	99·4	87·5
	1	0	5·4
	2	0·6	7·1
Pain	0	53·8	44·6
	½	24·7	26·1
	1	19·0	23·9
	2	1·9	5·4
Tenderness	0	36·1	22·3
	½	39·9	43·5
	1	20·2	28·8
	2	3·8	5·4

* Number of volunteers.

Local reactions

Erythema, pain and tenderness were analysed in the same way as previously.

The dose of *Invirin* recommended by the manufacturers is 1·0 ml. and this contains five times as much antigen as a dose of adjuvant vaccine. However, the presence of the oily vehicle and the intramuscular site of deposition of the adjuvant vaccine might be expected to offset the reduction in reactions caused by the smaller amount of antigen.

The adjuvant vaccine was not associated with erythema and the full, 1·0 ml., dose of *Invirin* caused less reddening of the skin than the half-dose given previously. About half those inoculated complained of pain and the arms of two-thirds or more were tender. *Invirin* elicited complaints of both pain and tenderness from a greater proportion of the volunteers than adjuvant vaccine and in both instances this excess is found in the early examinations. *Invirin* in general was associated with a larger incidence of reactions and caused them more rapidly but for rather a shorter time. By 7 days, however, there were no complaints of pain but 10 of tenderness (3 %) from all the volunteers.

As in the first part of the trial induration and swelling were only found in a few

https://doi.org/10.1017/S0022172400046027 Published online by Cambridge University Press

volunteers (four and two, respectively) and all occurred following *Invirin*. Bruising at the inoculation site, however, occurred more frequently with the adjuvant vaccine (eight cases) than with *Invirin* (four). This was possibly because of the different mode of inoculation. One student suffered transient symptoms in the distribution of the radial nerve after intramuscular injection of adjuvant vaccine.

No chronic swellings, induration or cystic lesions referable to the adjuvant were found either in those who had received this vaccine a month after inoculation or in any of the 143 of 158 volunteers of this group examined 8 months later.

Systemic reactions

It was difficult to detect any unequivocal pattern of these. There were 12 reports of coryzal symptoms among those given *Invirin*, and seven after adjuvant vaccine ($0{\cdot}4 > P > 0{\cdot}3$). In addition, one case of migraine, two of headache and two of malaise occurring within 3 days of inoculation were all within the group given *Invirin*. However, as this disparity of cases of coryza and other constitutional symptoms was also present at 7 and 28 days after inoculation the relation of these symptoms to the vaccines is not clear.

None of the volunteers said that the inoculation had interfered with work, play or social activities.

Table 4. *The replies to the question, 'Was the inoculation worth while?' at the end of each part of trial* 1

	Trial 1			
	First part		Second part	
Answers	Placebo 0·5 ml., 186* (%)	*Invirin* 0·5 ml., 194* (%)	Adjuvant vaccine 0·25 ml., 158* (%)	*Invirin* 1·0 ml., 184* (%)
'Yes	80·0	84·5	67·7	67·9
'No'	3·8	4·6	8·2	11·4
'Don't know'	10·2	7·7	10·8	9·8
No answer recorded	6·0	3·1	13·3	10·9

* Numbers of volunteers in each group.

General responses

In both parts of the trial, at the time of the final examination, 3 and 4 weeks after the inoculation respectively, the volunteers were asked whether they thought the inoculation would be worth while if it prevented influenza. In neither part of the trial did the answers distinguish between the different inocula, but there was a significant difference between the responses to the first and second parts of the study ($0{\cdot}025 > P > 0{\cdot}01$).

Those volunteers who had been in both parts of the trial were asked how the two inoculations received compared. No significant preference was revealed for one vaccine over another ($0{\cdot}7 > P > 0{\cdot}6$) or for placebo over vaccine.

Second trial (November 1963–February 1964)

There were 97 volunteers in this trial of whom 29 were nurses.

Local reactions

The incidence of reactions associated with the use of adjuvant vaccine in the first trial and *Admune* in the second were broadly similar regarding erythema

Table 5. *The distribution of replies when volunteers who had participated in both parts of the trial were asked, 'How did the second inoculation compare with that of the first part of the trial?' (trial* 1)

	First inoculation 0·5 ml. placebo. Second part inocula		First inoculation 0·5 ml. *Invirin*. Second part inocula	
Answers	Adjuvant vaccine 0·25 ml., 73* (%)	*Invirin* 1·0 ml., 88* (%)	Adjuvant vaccine 0·25 ml., 83* (%)	*Invirin* 1·0 ml., 95* (%)
'Better'	28·8	20·45	28·9	33·7
'Worse'	39·7	44·3	36·1	35·8
'Don't know'	12·3	14·8	18·1	18·9
No recorded answer	19·2	20·45	16·9	11·6

* Number of volunteers in each group.

Table 6. *The incidence of the main local reactions associated with the second trial compared with the corresponding data from the first trial*

		Second day		Seventh day	
Reaction		*Admune* adjuvant vaccine, second trial, 97* (%)	Adjuvant vaccine, first trial, 143* (%)	*Admune* adjuvant vaccine, second trial, 96* (%)	Adjuvant vaccine, first trial, 154* (%)
Erythema	0	95·9	99·3	100·0	100·0
	1	3·1	—	—	—
	2	1·0	0·7	—	—
Pain	0	63·9	76·0	99·0	100·0
	½	20·6	12·7	—	—
	1	14·4	10·6	1·0	—
	2	1·0	0·7	—	—
Tenderness	0	56·7	53·5	96·9	98·7
	½	23·7	33·1	1·0	1·3
	1	15·5	9·9	2·1	—
	2	4·1	3·5	—	—
Bruising	0	92·7	94·4	92·7	98·1
	½	2·1	2·1	1·0	0·6
	1	8·2	2·8	5·2	1·3
	2	4·1	0·7	1·0	—

* Number of volunteers in each group.

https://doi.org/10.1017/S0022172400046027 Published online by Cambridge University Press

($P = 0{\cdot}16$), pain ($0{\cdot}2 > P > 0{\cdot}1$) and tenderness ($0{\cdot}2 > P > 0{\cdot}1$). However, in the second trial more complaints of pain were recorded from the nurses than from the students.

Bruising was much more marked in the second trial, and, in the main, this was accounted for by the high incidence among the nurses. This might have been associated with the use of larger gauge needles for inoculating this group.

Transient swelling of the inoculated arm was reported by three nurses and three medical students.

Miscellaneous complaints included one, from a nurse, of mild regional axillary lymphadenitis for 2 days after inoculation. At 28 days another nurse reported some residual stiffness in the inoculated arm. On examination no objective sign was found.

In three of the nurses and in one student, all women, subcutaneous nodules at the site of inoculation were detected at the examination at 28 days. These nodules were fairly well defined and slightly tender on pressure. They were separate from the skin and underlying muscle and first appeared about 2 weeks after inoculation. On follow-up, one had disappeared 2 months after inoculation. In the other three, the nodules regressed slowly, and by 6 months were barely detectable.

Systemic reactions

No allergic manifestations were reported or seen. Inoculation was followed by a feeling of faintness in one case, and a nurse reported that a 'cold' started on the evening of the inoculation. Two volunteers complained of attacks of nausea and vomiting starting 24–36 h. after the inoculation. In one case, these symptoms also occurred in unvaccinated home contacts.

General responses

Of 96 volunteers questioned on the 7th day, nine said that the inoculation had troubled or hindered them. Eight of these were nurses. All graded the nuisance as 'slight'. Although none of the volunteers felt that the inoculation had curtailed work, play or social activities, two of the male students said they would not be inoculated again—because they never got influenza!

DISCUSSION

The evidence above shows that standard doses of aqueous and adjuvanted influenza vaccine caused a substantial number of local reactions. If those persons who had only minimal pain and tenderness are discounted, 1·0 ml. of *Invirin* caused about the same incidence of local reactions as recorded by Clarke (1962). The adjuvant vaccine, in comparison, caused rather fewer reactions; a finding which agrees with Howell & Mackenzie (1964).

On the other hand, although Clarke (1962) found 30% had general malaise and 6% allergic reactions and Howell & Mackenzie (1964) reported that influenza-like symptoms soon after injection and malaise persisting for a fortnight occurred in 9·8 and 22·4% of those given adjuvant and 8·5 and 22·4% of those given

aqueous vaccine respectively, in our experience systemic reactions were not a problem.

The authors of many reports have found it difficult to assess the acceptability of vaccines, particularly against less dreaded diseases, in objective terms. In the current trials the incidence of pain and tenderness revealed objectively did not correspond with the paucity of those who said the inoculations curtailed activities. However, the fact that nurses, doing more manual work, were more affected than students and the increased proportion of students denying the 'worthwhile'-ness of vaccine after a second inoculation tend to reinforce doubts (Howell & Stott, 1964, Richardson & Kilpatrick, 1964) whether an average population would support a programme of annual re-inoculation.

In addition, as children are particularly prone to reactions (Davenport & Hennessy, 1960), much less irritant vaccines would be needed to attempt the logical step of controlling influenza epidemics by vaccinating schoolchildren. The purified haemagglutinin vaccine described by Davenport *et al.* (1964) could well provide a more acceptable product.

The oil adjuvant vaccine presented a problem of its own. The occurrence of persistent nodules in some of our volunteers and an incidence of cysts of 3·3/10,000 in the Medical Research Council (1964) trial contrast with the earlier, more optimistic, reports (Himmelweit, 1960; Meiklejohn, 1962). For vaccination that is liable to be repeated and particularly for a disease of the nature of influenza such local reactions are not acceptable (Tyrrell, 1966). Also, with so small a dose of antigen much of the pain and tenderness associated with the inoculation was probably due to the adjuvant components themselves. McCarthy (1964), using hexadecane and octadecane, has demonstrated the ability of mammals to metabolize preparations of straight-chain hydrocarbons given orally. However, from the observed persistence of oil at the site of adjuvant inoculations this breakdown must occur slowly in the tissues and possibly the equivalent fatty acids that are formed during metabolism may themselves be irritant just as the greater toxicity of early batches of adjuvant was due to excess free oleic acid in the emulsifying agent.

Several approaches to solve this difficulty have been made. Wilner *et al.* (1963), in limited experiments, found that a pure branched-chain hydrocarbon oil produced a better adjuvant effect than the usual Drakeol 6VR with less toxicity. Workers at the Merck Institute (Woodhour *et al.* 1964; Peck *et al.* 1964) have reported on the efficacy of a metabolizable adjuvant comprising peanut oil, aluminium monostearate and Arlacel A and found in animal experiments that the reactions produced were quantitatively less than with mineral oil. Herbert (1965) described a 'multiple emulsion' in which the adjuvant emulsion was dispersed in fine droplets in an aqueous phase and thus might be less able to cause cysts. It is likely that one, or a combination of these developments, may lead to more acceptable adjuvant vaccines.

While the vaccines used in the trials did not cause many systemic reactions they are clearly not entirely satisfactory but there is evidence that better products may be forthcoming.

SUMMARY

Trials of aqueous and oil adjuvant vaccines in young adult volunteers showed that severe local reactions were rare. However, the incidence of minor symptoms was too high for a vaccine which requires to be administered repeatedly. In contradistinction to some reports, systemic and allergic reactions did not constitute a problem.

I should like to thank my colleagues at the Department of Microbiology for their assistance in inoculating, bleeding and checking reactions in the volunteers. Without the co-operation of the volunteers this study would not have been possible. I also wish to thank Prof. G. W. A. Dick for his encouragement and advice, and Mr T. D. Merrett, who kindly gave advice on the statistical analysis of the results. The vaccines and placebo were supplied by Glaxo Laboratories Ltd., and financial assistance for the study came from the Northern Ireland Hospitals Authority and the National Fund for Research into Poliomyelitis and other Crippling Diseases.

REFERENCES

Beebe, G. W., Simon, A. H. & Vivona, S. (1964). Follow-up study on army personnel who received adjuvant influenza virus vaccine 1951–53. *Am. J. med. Sci.* **247**, 385.

Clarke, E. G. (1962). Vaccination against influenza. *Br. med. J.* ii, 734.

Cope, J. (1960). Influenza vaccination. *Br. med. J.* i, 423.

Davenport, F. M. & Hennessy, A. V. (1960). Prevention of influenza in childhood by vaccination: Principles, problems and progress. In *Viral Infections of Infancy and Childhood*, p. 145. Ed. H. M. Rose, New York: Hoeber-Harper.

Davenport, F. M., Hennessy, A. V., Brandon, P. M., Webster, R. C., Barrett, D. D. Jr. & Lease, G. O. (1964). Comparisons of serologic and febrile responses in humans to vaccination with influenza A viruses or their hemagglutinins. *J. Lab. clin. Med.* **63**, 5.

Francis, T. Jr. & Magill, T. P. (1935–6). Vaccination of human subjects with virus of human influenza. *Proc. Soc. exp. Biol. Med.* **33**, 604.

Francis, T. Jr. & Magill, T. P. (1937). The antibody response of human subjects vaccinated with the virus of human influenza. *J. exp. Med.* **65**, 251.

Griffin, H. E. (1959). Reactions to influenza vaccine. *Ann. Allergy* **17**, 179.

Henle, W. & Henle, G. (1945). Effect of adjuvants on vaccination of human beings against influenza. *Proc. Soc. exp. Biol. Med.* **59**, 179.

Herbert, W. J. (1965). Multiple emulsions, a new form of mineral-oil adjuvant. *Lancet* ii, 771.

Himmelweit, F. (1960). Serological responses and clinical reactions to influenza virus vaccines. *Br. med. J.* ii, 1690.

Hirst, G. K., Rickard, E. R. & Friedewald, W. F. (1944). Studies in human immunization against influenza. Duration of immunity induced by inactive virus. *J. exp. Med.* **80**, 265.

Howell, R. W. & Mackenzie, A. B. (1964). A comparative trial of oil-adjuvant and aqueous polyvalent influenza vaccines. *Br. J. ind. Med.* **21**, 265.

Howell, R. W. & Stott, A. N. B. (1964). A trial of oil-adjuvant influenza vaccine in a non-epidemic season. *Br. J. ind. Med.* **21**, 259.

McCarthy, R. O. (1964). Mammalian metabolism of straight-chain saturated hydrocarbons. *Biochim. biophys. Acta* **84**, 74.

Medical Research Council (1964). Clinical trials of oil-adjuvant influenza vaccines, 1960–63. *Br. med. J.* ii, 267.

Meichen, F. W., Rogan, E. & Howell, R. W. (1962). A study of the effectiveness of influenza vaccination in an industrial population. *Br. J. ind. Med.* **19**, 203.

Meiklejohn, G. (1962). Adjuvant influenza adenovirus vaccine. *J. Am. med. Ass.* **179**, 594.

Norwood, W. O. & Sachs, R. R. (1947). The protective effect of vaccination against epidemic influenza B in an industrial plant. *Ind. Med.* **16**, 1.

PECK, H. M., WOODHOUR, A. F., METZGAR, D. P., MCKINNEY, S. E. & HILLEMAN, M. R. (1964). New metabolizable immunologic adjuvant for human use. 2. Short-term animal toxicity tests. *Proc. Soc. exp. Biol. Med.* **116**, 523.

RICHARDSON, L. M. & KILPATRICK, S. J. (1964). Influenza immunization. A three year study in a factory population. *Med. Offr.* **111**, 5.

SALK, J. E. (1948). Reactions to influenza virus vaccines. *J. Immun.* **58**, 369.

TYRRELL, D. A. (1966). Influenza virus vaccines. *Prescriber's J.* (*Australian edition*) **5**, 51.

WILNER, B. I., EVERS, M. A., TROUTMAN, H. D., TRADER, F. W., & MCLEAN, I. W. JR. (1963). Vaccine potentiation by emulsification with pure hydrocarbon compounds. *J. Immun.* **91**, 210.

WOODHOUR, A. F., METZGAR, D. P., STIM, T. B., TYTELL, A. A. & HILLEMAN, M. R. (1964). New metabolizable immunologic adjuvant for human use. I. Development and animal immune response. *Proc. Soc. exp. Biol. Med.* **116**, 516.