SESSION V

FUTURE INFLUENZA VIRUS VACCINES

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Adjuvant Influenza Vaccines

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Emulsified inactivated influenza vaccines have been in use for some 18 years and the goal of enhanced serological response lasting 2 years or more has been attained. The safety of the method in relation to immediate pyrogenic reactions has been demonstrated and no carcinogenic effects are known to have occurred in man. However, the problem of delayed local reactions after the injection of mineral-oil vaccines has not been solved. British experience of adverse reactions to commercial adjuvant influenza vaccine is quoted.

New methods for obtaining adjuvant action without the risk of local abscess formation are needed both for inactivated whole virus and for split haemagglutinin vaccines. Reversal of water-in-mineral-oil emulsion to oil-in-water emulsion reduces viscosity and permits diffusion of the depot injection. A trial in Britain has shown equally good adjuvant properties of the reversed emulsion incorporating influenza virus vaccine so far as serological response is concerned, although it has not yet been conducted on a scale that would allow of adequate evaluation of the likelihood of delayed local reactions.

The fact that adjuvant vaccines are listed for consideration in a session dealing with the future can only mean that available adjuvant materials possess drawbacks. As mineral-oil adjuvant vaccines containing Drakeol and Arlacel A are the only adjuvant influenza vaccines which have been used on a very large scale and for a long period of time, it is likely that at least with these materials the principal disadvantages are now known. In fact, 2 of the risks involved in the use of mineral-oil adjuvant vaccines still lack substance in relation to man. I refer to the theoretical possibility of carcinogenicity which was suggested by the experimental induction of tumours in BALB/C mice by Lieberman, Mantel & Humphrey (1961) and Potter & Boyce (1962), and in DBA/2 mice by Rask-Nielsen & Ebbesen (1965) using mineral oil intraperitoneally. The follow-up by Beebe, Simon & Vivona (1964) of some 44 000 men in the US Armed Forces, of whom 18 000 received adjuvant influenza vaccine, is therefore of considerable importance. No suggestion of enhanced incidence of tumours was found in the mortality of these men during the 9 years following immunization.

Secondly, sensitization to materials contained in adjuvant influenza vaccine is a theoretical possibility in the case of extraneous substances such as penicillin and also with antigens of the blood group substances. Beebe and others (1964) found some evidence of increased sensitivity to penicillin leading to urticaria, particularly in those receiving vaccine in the early 1950s when it was manufacturing practice in the USA to add penicillin to the eggs from which vaccine was made. Iso-immunization by blood-group A substance has been a theoretical risk with all varieties of influenza vaccine since the demonstration of this antigen in commercial influenza vaccine by Springer & Tritel (1962). Springer & Schuster (1964), indeed, found that extracts of influenza vaccine induced increased iso-agglutinin titres in inoculated persons but others have failed to find such unwanted antibody induction after ordinary saline or commercial oil-adjuvant vaccines (Forsyth & Wilson, 1968).

There remain the unwanted local reactions variously described as cysts (Bell et al., 1961) or chemical abscesses. Beebe, Simon & Vivona (1964) found evidence of these delayed local nodules in the follow-up of Army personnel but the incidence was too low to affect widespread use of mineral-oil vaccine in the US Armed Forces. Indeed, Davenport (1968) recently described 17 years' experience with adjuvant influenza vaccines and urged their adoption generally in the USA.

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BRITISH EXPERIENCE WITH MINERAL-OIL ADJUVANT VACCINES

This has been of two sorts. First, the Medical Research Council's Committee on Clinical Trials of Influenza Vaccine (1955) and Committee on Influenza and Other Respiratory Virus Vaccines (1964) have carried out both small- and large-scale trials of mineral-oil vaccines since 1953. Evidence has been obtained both of the high and sustained antibody responses which they produce and also of their protective efficacy. In these trials local and general febrile reactions have always been less in frequency than after the use of ordinary saline vaccine. But delayed nodular reactions occasionally leading to liquefaction and tracking through the tissues have been seen in a low percentage of inoculated persons. The figure in the later trials was 3.3 per 10 000 persons but only a proportion of these developed nodules which required surgical aspiration or incision.

The second experience in Britain arose from commercial sale of the vaccine between 1963 and 1965, when some 1.3 million doses of mineral-oil influenza vaccine containing Drakeol and Arlacel A were released. An estimated 900 000 doses were administered and during 1964 and 1965 some 40 delayed adverse reactions came to the notice of the Safety of Drugs Committee in the United Kingdom and to manufacturers. It is possible that further unreported reactions actually occurred but unlikely that serious reactions were missed. In fact, only 9 instances of reactions requiring local surgical procedures were known. However, this number was sufficient for the vaccine to be voluntarily withdrawn by the manufacturers except for use in special-risk groups of the population. This experience, coming on the heels of the reactions reported from the use of adjuvant tetanus toxoid in New Guinea (Pittman, 1967) and of mineral-oil adjuvant cholera vaccine in the Philippines (Ogonuki, Hashizume & Abe, 1967), led to a halt in the exploitation of mineral-oil vaccines in Britain.

The mechanism of these adverse local reactions has, however, remained obscure. In spite of many attempts to induce delayed local reactions in experimental animals, no success has been obtained. Histological examination of 4 human nodules in Britain showed granulomata resembling sarcoid lesions. Others (Ogonuki, Hashizume & Abe, 1967) have regarded the granulomata as being due to reactions of the foreign-body type.

REVERSED OR MULTIPLE ADJUVANT VACCINE

In 1965, Herbert (1965) described a method of treatment of mineral-oil adjuvant vaccine containing Drakeol and Arlacel A which caused the previous water-in-oil emulsion to pass into an oil-in-water dispersion. Herbert found that Tween 80 and ultrasonic dispersion caused the emulsion to become less viscous and consequently to disperse in the subcutaneous tissues more readily. Experimental immunization suggested no impairment of the antigenicity of the vaccine in its new phase and Herbert (1967) reported that the emulsions were very stable. A clinical trial under the auspices of the Medical Research Council's Influenza Vaccine Committee was organized in 1966 and Taylor and others (1969) have just reported on its results. The vaccine contained 2 A2 and 2 B influenza viruses. Table 1 shows that the trial was a serological one involving 302 persons and using 2 mineral-oil emulsion vaccines—one water-in-oil (simple) emulsion, one prepared by the Herbert process—and for controls a saline influenza vaccine and a tissue culture rhinovirus vaccine. Local and systemic reactions were reported as shown but the systemic reactions were mild and no delayed local reactions were noted. Table 2 shows that the distributions of antibody titres before immunization were similar in the various groups though, as shown in Table 3, persons with a history of previous immunization with oil-adjuvant vaccines had higher titres than those previously unvaccinated. Table 4 shows the geometric mean titres in the

TABLE 1

LOCAL AND SYSTEMIC REACTIONS UP TO 72 HOURS AFTER VACCINATION, ACCORDING TO VACCINE GROUP [a]

Type of reaction	Number [b] showing reactions after			
	Aqueous vaccine	Simple emulsion vaccine	Multiple emulsion vaccine	Rhinovirus vaccine (control)
Local	6 (8)	6 (8)	20 (26)	0
Systemic	21 (27)	27 (36)	29 (38)	10 (14)
No reaction	51 (65)	41 (55)	27 (36)	64 (86)
Total	78	74	76	74

[a] Reproduced, by permission, from Taylor et al. (1969).
[b] Figures in parentheses indicate percentages.

TABLE 2

ANTIBODY TITRES BEFORE VACCINATION ACCORDING TO VACCINE GROUP [a]

Vaccine group	No.	Range of antibody titres (haemagglutination-inhibition)							
		<12		12–48		>48		Geometric mean titres	
		A2	B	A2	B	A2	B	A2	B
Aqueous	41	20	27	15	11	6	3	16	10
Simple emulsion	39	17	24	12	12	10	3	20	12
Multiple emulsion	42	18	27	19	13	5	2	17	10
Rhinovirus (control)	40	16	24	12	12	12	4	25	13

[a] Reproduced, by permission, from Taylor et al. (1969).

TABLE 3

ANTIBODY TITRES IN FIRST SERUM SAMPLE ACCORDING TO HISTORY OF PREVIOUS INFLUENZA VACCINATION [a]

Group	Total no.		HI antibody titres [b]					
			<12		12–48		>48	
	A2	B	A2	B	A2	B	A2	B
Previously vaccinated	53	53	5 (9)	18 (34)	22 (42)	24 (45)	26 (49)	11 (21)
Not previously vaccinated	109	109	66 (61)	84 (77)	36 (33)	24 (22)	7 (6)	1 (1)

[a] Reproduced, by permission, from Taylor et al. (1969).
[b] Figures in parentheses indicate percentages.

TABLE 4

GEOMETRIC MEAN OF ANTIBODY TITRES IN SERUM SAMPLES TAKEN IMMEDIATELY BEFORE VACCINATION (1st), APPROXIMATELY 3 MONTHS AFTER VACCINATION (2nd) AND APPROXIMATELY 12 MONTHS AFTER VACCINATION (3rd) [a]

Vaccine group	No.	Geometric mean titre (HI)					
		A2			B		
		1st	2nd	3rd	1st	2nd	3rd
Aqueous	41	16	171	102	10	34	23
Simple emulsion	39	20	334	166	12	89	52
Multiple emulsion	42	17	461	206	10	132	70
Rhinovirus (control)	40	25	26	25	13	13	12

[a] Reproduced, by permission, from Taylor et al. (1969).

various groups of persons before and 3 and 12 months after immunization. The superiority and comparability of the emulsion vaccines was clearly demonstrated and there was no evidence of reduction of antigenicity after the redispersion of the mineral-oil vaccine. A larger trial is now being planned, partly to obtain evidence concerning reactions. Because both Drakeol and Arlacel A are still present in the vaccine, the Safety of Drugs Committee has refused to sanction other than limited trials.

THE FUTURE

It is quite obvious that so long as there is any question of using inactivated whole influenza vaccine or a split product subcutaneously, methods of enhancing the antibody response are still much to be desired. Hilleman's experiences with a metabolizable vegetable-oil adjuvant vaccine (Woodhour et al., 1964) containing Arlacel have been published and no additional comment can be made. Other adjuvant materials have been used, some successfully and some unsuccessfully. Fukumi (1967) has used a vegetable oil (sesame) with influenza vaccine though he found it had less immunizing capacity than mineral-oil vaccine, as was the British experience with peanut oil.[1] Holt (1967) has successfully used squalane (prepared from shark-oil) and Arlacel with triple diphtheria, tetanus and pertussis vaccine. The emulsions were absorbed on aluminium-phosphate gel. Such emulsions do not seem to have been tested with influenza vaccine.

It seems that aluminium phosphate is not an adequate adjuvant for influenza haemagglutinin according to Davenport, Hennessy & Askin (1968), though Davenport & Hennessy (1967) were able to obtain adjuvant effects when haemagglutinin was suspended as a water-in-oil emulsion with mineral oil. Experimentation with aluminium-oxide or aluminium-hydroxide gel as adjuvants for inactive viral vaccines such as poliovaccine (Drescher, Grützner & Godglück, 1967) or influenza vaccine (Schmidt, 1967) suggest that there is still much to be learnt.

Perhaps it would be as well to end on a note of caution. The history of the use of drugs in man indicates the great need for caution before risks are dismissed as negligible. Until a fuller understanding of the mechanism of adjuvant action has been obtained, it is clear that unusual and unwanted effects may continue to occur whatever the materials which are used. However, adjuvant vaccines seem certain to have a future in programmes of human immunization and further basic research work is necessary.

[1] Pollock, T. M.—unpublished report, 1967, to the Medical Research Council's Committee on Influenza and Other Respiratory Virus Vaccines.

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