Patients harbouring slowly growing tumours or tumours of the reticulo-endothelial system are likely to do well provided they have not progressed to a complete neurological lesion. Those with less favourable tumours will do badly, though the results may be improved by earlier and more vigorous treatment. Most of the patients with carcinoma of the bronchus in this series presented with severe or complete spinal-cord lesions. In such rapidly growing tumours speed of decompression of the cord is of vital significance to the final result. Similarly patients suffering abrupt spinal-cord lesions are unlikely to improve unless operated on within a few hours of the incident occurring. Patients with tumours situated on the posterior aspect of the theca will often do well, while anterior compression is of more sinister significance. No significant improvement by any form of therapy can be expected in patients who have suffered a complete spinal-cord lesion even if caused by the most favourable of these malignant tumours. Patients who show clinically obvious visceral metastases are unlikely to live long enough to benefit from treatment. Loss of bladder function even for several days does not necessarily indicate a poor prognosis.

No assessment of the relative merits of various forms of therapy can be given. All the patients under consideration were treated by a laminectomy soon after admission, often followed by other appropriate measures, including irradiation and hormone and chemical therapy. Many patients showing little improvement after laminectomy did not receive further treatment. There was no standard pattern from which conclusions could be drawn.

Surgery has the advantages of providing rapidly both a histological diagnosis and a decompression of the spinal cord. It also enables the clinician to distinguish with certainty between the diseases under consideration and other more benign forms of spinal-cord compression. It can do no more ; the treatment of the underlying disease is in the hands of the radiotherapist or physician.

Summary

A series of 145 patients with spinal-cord compression from verified extradural malignant tumours has been presented. All were treated by laminectomy, often supplemented by other forms of treatment.

There was an operative mortality rate of 6%. Ten patients deteriorated after operation. Forty-four patients improved sufficiently and for an adequate period of time to justify the treatment given. Various prognostic factors are discussed.

Earlier diagnosis and treatment appear to offer the only hope of improving a rather unsatisfactory position.

Our thanks are due to the British Empire Cancer Campaign for a grant to one of us (J. G. B.) which made this study possible. We are also indebted to Mr. L. S. Walsh and Mr. A. E. Richardson of the Neurosurgical Department of St. George's Hospital at Atkinson Morley's Hospital for their help and permission to publish cases under their care. Our thanks are finally due to the secretarial staff for their invaluable help.

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Prevention of Colds by Vaccination Against a Rhinovirus

A Report by the Scientific Committee on Common Cold Vaccines*

Brit. med. J., 1965, **1**, 1344–1349

Rhinoviruses can be isolated from 20 to 30% of adults with common colds (Hamre and Procknow, 1963), and therefore a successful rhinovirus vaccine would be a significant means of protection against this disease. Previous work at the Common Cold Research Unit has shown that specific antibody production can be stimulated by live or formalin-inactivated M strain rhinoviruses[1] (Doggett *et al.*, 1963), but it was not shown how long this antibody persisted or whether it would prevent colds. As there are many strains of rhinoviruses which are serologically distinct, a polyvalent vaccine would be necessary to ensure protection against infection with these viruses. Attempts have therefore been made to show that vaccination with a rhinovirus confers specific immunity to infection, and also to concentrate virus, and to enhance antibody responses by combining virus with adjuvant in the hope of finding a method by which several viruses might be concentrated into a small volume of inoculum and produce a large antibody response.

Materials and Methods

Three M strain rhinoviruses were used in the experimental vaccines—namely, H.G.P., and a serologically identical strain,

* The members of the Committee are: Sir Christopher Andrewes (chairman), Dr. D. A. J. Tyrrell (secretary) (M.R.C. Common Cold Research Unit), Dr. P. B. Stones (Pfizer Limited), Dr. A. J. Beale and Dr. R. D. Andrews (Glaxo Group Limited), Dr. D. G. ff. Edward and Dr. A. P. Goffe (Wellcome Foundation Limited), Miss Jennifer E. Doggett (M:R.C. Common Cold Research Unit), Dr. R. F. Homer and Mr. R. S. Crespi (National Research Development Corporation), Dr. E. M. B. Clements (Medical Research Council).

The report was prepared by Miss J. E. Doggett.

The Common Cold Vaccine Scientific Committee is the body which co-ordinates the research work being undertaken in this field within the previously announced collaboration between the Medical Research Council, Glaxo Group Limited, Pfizer Limited, the Wellcome Foundation Limited, and the National Research Development Corporation.

[1] M strain rhinoviruses grow in monkey-kidney cells in addition to human embryonic tissue and human malignant cells, in contrast with H strain rhinoviruses, which grow only in human embryonic tissues and human malignant cells. The virus originally described as E.C.H.O. virus type 28 is now agreed to be an M rhinovirus and not an enterovirus ; the original name is retained in this paper as no alternative name has yet received general approval.

P.K., and "E.C.H.O. 28" which is serologically distinct from H.G.P.

Live P.K. vaccine was prepared as described earlier in human embryo-kidney cells (Doggett *et al.*, 1963) from virus which had had seven passages in human embryo-kidney cultures after initial isolation.

Formalin-inactivated H.G.P. virus vaccine was prepared by Pfizer Limited. Virus pools were prepared in monkey-kidney cells and inactivated with 1/4,000 formalin for six days at 37° C. Some formolized E.C.H.O. 28 vaccine was also supplied by Dr. Holper (Abbott Laboratories). An H strain, D.C. (Tyrrell *et al.*, 1962), was also used.

Volunteers were challenged with either P.K. virus or E.C.H.O. 28 in the form of nasal washings from experimentally or naturally infected subjects. The virus used had never been passed in tissue cultures, and its identity was checked by neutralization with specific immune serum.

Tissue Cultures.—Human diploid fibroblast cell strains were prepared from embryo lungs as described by Hayflick and Moorhead (1961). Cultures were maintained in Eagle's minimal essential medium (Burroughs Wellcome) with 2% calf serum: 0.09% $NaHCO_3$ was added, the medium having a *p*H of about 7. After inoculation cultures were rolled at 33° C. Preparation and maintenance of monkey-kidney cultures have been described earlier (Tyrrell and Parsons, 1960).

Virus Isolations and Neutralization Tests.—Virus isolations were made from nasal washings inoculated into monkey-kidney cultures (Tyrrell and Parsons, 1960) or human diploid fibroblast cells (Hayflick and Moorhead, 1963). The medium was changed 24 hours after inoculation. Virus isolations from the majority of volunteers were identified by a neutralization test with specific antiserum. Neutralization tests were carried out in monkey-kidney cultures or human diploid fibroblast cells by the microplaque reduction technique (Taylor-Robinson and Tyrrell, 1962) or by an end-point technique, using 60–120 TCD_{50} of virus.

Volunteers.—Volunteers at the Common Cold Research Unit were housed and observed as described by Andrewes (1948). Serological studies were also carried out on groups of adult volunteers who were not in isolation.

Results

Experiments on the use of adjuvants were carried out in an attempt to reduce the volumes of each antigen required in a polyvalent vaccine.

Combination of Rhinoviruses with Mineral Oil Adjuvant

The mineral oil adjuvant Drakeol-Arlacel was used in the first set of experiments. It was kindly supplied by Dr. F. Himmelweit, who had shown that this particular batch was an efficient adjuvant when used with influenza virus. High and persisting antibody levels could be obtained with a tenth of the amount of influenza virus that would have been needed in an aqueous vaccine (Himmelweit, 1960).

Equal volumes of Drakeol-Arlacel and live P.K. virus in infected tissue culture fluid were emulsified together by means of a needle and syringe. If the emulsion was centrifuged at 2,000 r.p.m. for five minutes it did not break down. 0.6–0.9 ml. of emulsion was inoculated intramuscularly into seven volunteers who were bled at the time of inoculation and two and six weeks later. The antibody responses of these volunteers were compared with those of nine others who had received 1 ml. of the same pool of P.K. virus as an intramuscular injection and were bled at the time of inoculation and two weeks later (Fig. 1). Initial serum antibody levels (K value) were similar in both groups; the geometric mean titre (G.M.T.) being 1.22 in the group receiving emulsified vaccine, and 1.65 in the group receiving non-emulsified vaccine. Five out of seven volunteers given emulsified vaccine and eight out of nine given non-emulsified vaccine had rises in neutralizing antibody to P.K. virus. The antibody responses of those given emulsified vaccine were delayed, showing that Drakeol-Arlacel was having some effect, but the final antibody levels of this group (G.M.T. 4.96) were lower than in the group given non-emulsified vaccine (G.M.T. 17.5); it must be noted, however, that the emulsion contained rather less than half the volume of culture fluid given to the second group of volunteers.

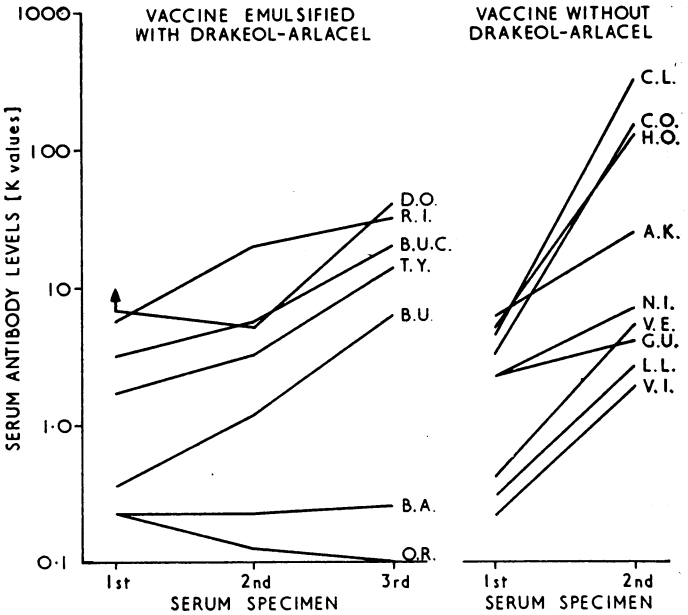

FIG. 1.—Antibody responses of seven volunteers given P.K. vaccine emulsified with Drakeol-Arlacel, compared with those of nine volunteers given the same vaccine without Drakeol-Arlacel.

In further experiments formalin-inactivated E.C.H.O. 28 vaccine was emulsified with an equal volume of Drakeol-Arlacel. It was administered to volunteers in a single dose, four volunteers receiving 0.4 ml. and seven others 0.2 ml. each. Sixteen volunteers were given two doses of 1 ml. each without Drakeol-Arlacel. Two out of four volunteers each given 0.4 ml. of emulsified vaccine, and two out of seven each given 0.2 ml. of emulsified vaccine had rises in E.C.H.O. 28 antibody. Thirteen out of 16 volunteers given non-emulsified vaccine had rises in antibody, and resulting antibody titres were similar to or higher than those in the group receiving emulsified vaccine. It seemed that Drakeol-Arlacel had little adjuvant effect on the rhinovirus tested.

Aluminium Phosphate Precipitation

These experiments were designed to see if aluminium phosphate could be used as an adjuvant for rhinoviruses. Previous work had shown that the infectivity of rhinoviruses was almost completely adsorbed on to aluminium phosphate gel (K. H. Fantes and D. A. J. Tyrrell, unpublished). H.G.P., E.C.H.O. 28, and an H strain, D.C., were adsorbed on to aluminium phosphate by Dr. Fantes and inoculated intramuscularly into rabbits. Antibody responses occurred if the viruses were given either singly or as a trivalent vaccine (Table I). This showed that antigenicity, as well as infectivity, could be adsorbed on to aluminium phosphate. No adjuvant effect was detected when a weakly antigenic preparation of H.G.P. was inoculated into rabbits without treatment or after adsorption on to different amounts of aluminium phosphate (0.5–4 mg./ml.).

The effect of aluminium phosphate on antigenicity of rhinoviruses in man was then investigated. Formalin-inactivated

E.C.H.O. 28 vaccine was adsorbed on to aluminium phosphate (0.2 mg./ml.) at *p*H 6.9 and a 1-ml. intramuscular injection was given to five volunteers. The antibody responses of these volunteers were compared with those of six given 1 ml. of vaccine not adsorbed on to aluminium phosphate. Three responses occurred in the six volunteers given vaccine not adsorbed on to aluminium phosphate, while two occurred in the five given adsorbed virus. Final antibody levels in both groups were similar. There was therefore no evidence of an adjuvant effect of the aluminium phosphate in man, although the antigenic activity had apparently been adsorbed.

TABLE I.—*Antibody Responses of Rabbits Inoculated Intramuscularly with Rhinoviruses Adsorbed on to Aluminum Phosphate Gel*

Vaccine	Antibody Rises to:		
	H.G.P.	D.C.	E.C.H.O. 28
H.G.P.	3/3*	—	—
D.C.	0/3	3/3	—
E.C.H.O. 28	0/3	—	2/3
H.G.P. + D.C. + E.C.H.O. 28	3/3	3/3	2/3

* The numerator denotes the number with antibody rises; the denominator the number inoculated.

Challenge of Vaccinated Volunteers

Experiments to determine whether antibody produced in response to intramuscular injection of rhinoviruses protected against subsequent infection were carried out with formalin-inactivated H.G.P. vaccine prepared by Pfizer Limited. Previous work (Doggett *et al.*, 1963) had shown that formalin-inactivated virus produced as good an antibody response as live virus. Formalin-inactivated virus had two advantages over live virus for these experiments: firstly, any undetected simian viruses picked up from the monkey-kidney cultures might also be inactivated; and, secondly, the vaccine would be more stable for transporting than live vaccine.

Pilot serological studies showed that the vaccine was a good antigen, all 28 volunteers who received two doses of 1 ml. intramuscularly having threefold to fortyfold rises in antibody level.

In the present study volunteers received two 1-ml. doses at weekly intervals from their general practitioners. About two weeks later they were challenged with homologous virus P.K., or with heterologous virus, E.C.H.O. 28. Other volunteers who had not been vaccinated were given the same challenge virus or Hanks's saline. Nasal washings were collected daily from the second to fifth days after inoculation, and the volunteers were observed for clinical signs of infection. Sera were collected from vaccinated volunteers before vaccination and from vaccinated and unvaccinated volunteers before challenge and two weeks after challenge. Antibody levels were determined by an end-point neutralization test.

Antibody Responses to H.G.P. Vaccination

Forty volunteers received H.G.P. vaccine from their general practitioners. Fourfold antibody rises occurred in 35 of them after vaccination (Table II). Eighteen of the volunteers had no pre-existing antibody as determined by the end-point neutralization test (antibody level of less than 1/4), and all of these became seropositive. Seventeen of the 22 volunteers who had antibody before vaccination had rises in antibody levels. The vaccine was therefore as effective for producing antibody in subjects without antibody as in those who had pre-existing antibody.

TABLE II.—*Antibody Responses of Volunteers Given Two Intramuscular Injections of Formalin-inactivated H.G.P. Vaccine*

Initial Antibody Titre	No. of Volunteers	
	Vaccinated	With Fourfold Antibody Rise
< 1/4	18	18/18*
> 1/4	22	17/22
Total	40	35/40

* The numerator denotes the number with antibody rises; the denominator the number vaccinated.

Comparative neutralization tests on sera by the end-point method and the microplaque-reduction test showed that sera with any detectable antibody in the end-point test had K values greater than 0.2. It was concluded that a level of antibody detectable by the end-point method should be sufficient to protect against clinical infection (Bynoe *et al.*, 1961).

Results of Challenge with Homologous Virus

Twenty-eight vaccinated volunteers and 23 unvaccinated volunteers were challenged with 1 ml. of P.K. virus intranasally. The titre of the challenge virus was between $10^{1.9}$ and $10^{3.2}$ TCD /ml. One out of 28 vaccinated volunteers had a cold compared with 11 colds in 23 unvaccinated volunteers (Tables III and IV). No colds occurred in volunteers receiving Hanks's saline. Colds occurred in those volunteers who had low initial neutralizing antibody levels. Virus was isolated from 5 out of 28 vaccinated volunteers and from 14 out of 23 unvaccinated volunteers. In addition, herpes simplex virus was isolated from one vaccinated volunteer. Mild symptoms were noted in some volunteers who had no colds but from whom virus was isolated, especially in the group who received the higher dose of challenge virus. Antibody titres rose after challenge in at least 11 out of 27 vaccinated volunteers, compared with 15 out of 22 in the unvaccinated group. The responses in the vaccinated group were probably the result of challenge rather than delayed responses to vaccination, as H.G.P. antibody levels did not rise after challenging volunteers with intranasal E.C.H.O. 28 viruses (see below). There was therefore laboratory evidence of infection (virus isolation or antibody rise) in 13 out of 28 vaccinated volunteers and in 15 out of 23 unvaccinated volunteers. It can be concluded that the vaccine prevented illness and the shedding of virus but did not prevent subclinical infection with homologous virus.

Results of Challenge with Heterologous Virus

Mogabgab (1962) thinks that antibody responses to viruses causing respiratory diseases are so non-specific that vaccination with a few respiratory viruses would protect against a large number of related viruses causing respiratory illness. We have shown, however, that the antibody responses of human volunteers to a number of respiratory viruses are specific (Buckland *et al.*, 1964), and, in particular, that heterologous antibody responses to H.G.P. or E.C.H.O. 28 do not occur in volunteers inoculated with E.C.H.O. 28 or H.G.P. To collect more information on specificity of rhinovirus antibodies 13 volunteers who had been vaccinated with H.G.P. vaccine and 10 unvaccinated volunteers were challenged with 1 ml. of E.C.H.O. 28 intranasally ($10^{1.2}$ TCD /ml.). Six out of 13 vaccinated and 2 out of 10 unvaccinated volunteers developed colds (Tables V and VI). Virus was isolated from 11 of the 13 vaccinated volunteers and 8 of the 10 unvaccinated volunteers. Nine of 13 vaccinated volunteers and five of nine unvaccinated volunteers had E.C.H.O. 28 antibody rises after challenge, so that 11 out of 13 vaccinated and 9 out of 10 unvaccinated volunteers had laboratory evidence of infection with E.C.H.O. 28 virus. All vaccinated volunteers had rises in H.G.P. antibody but not E.C.H.O. 28 antibody after vaccination. No vaccinated volunteers challenged with E.C.H.O. 28 virus had post-challenge rises in H.G.P. antibody, showing that antibody responses to H.G.P. vaccination were completed before the time of challenge. It is also further evidence that E.C.H.O. 28 and H.G.P. infections do not give

rise to heterologous antibody production, and it can be concluded that vaccination of volunteers with this H.G.P. vaccine fails to protect them from infection with E.C.H.O. 28 virus.

Persistence of Antibody after Vaccination or Infection

Taylor-Robinson (1963) tested serial samples of serum from naturally infected subjects, and showed that naturally acquired antibody to M strain rhinoviruses persisted for several years. We wondered whether antibody stimulated by vaccination also persisted. We therefore obtained sera from volunteers who had been at the Common Cold Research Unit 12 to 18 months previously, when they had received live P.K. or H.G.P. virus intranasally or as an intramuscular vaccine. The neutralizing antibody levels in the sera were determined (Fig. 2), and a threefold rise or fall in serum K value was regarded as significant. There was one fall in the vaccinated group (volunteer S.M.) and none in the infected group. There was one antibody rise in each group (volunteers J. A. and Y. O.). All the antibody titres remained above the pre-vaccination or pre-infection levels and above a K value of 0.2, which has been shown to be capable of protecting against infection with this virus (Bynoe *et al.*, 1961). Antibody therefore seems to persist for 12 to 18 months, and to do so as well after vaccination as it does after experimental infection. Antibody levels may well be maintained by infections with the same virus or related viruses. Subclinical infections in the presence of large amounts of antibody have been demonstrated in this present study in the volunteers who received H.G.P. virus vaccine and who were challenged with homologous virus.

Discussion

Mufson *et al.* (1963) vaccinated volunteers with a formalin-inactivated E.C.H.O. 28 vaccine and challenged them with E.C.H.O. 28 virus. Eleven out of 22 volunteers developed colds on challenge. Similar results were obtained in some unpublished experiments referred to earlier (Doggett *et al.*, 1963), using a live P.K. vaccine. Eleven volunteers were vaccinated; on

TABLE III.—*Result of Challenge with H.G.P.-like Virus (P.K.) in Vaccinated Volunteers*

Volunteer	Challenge Dose	Cold or Symptoms	Virus (P.K.) Isolations on Day				Reciprocal of H.G.P. Antibody Titre in Sera*			H.G.P. Fourfold Antibody Rise	
			2	3	4	5	1st	2nd	3rd	Post-vaccination	Post-challenge
J.B. ..	$10^{1.9}TCD_{50}$	0	0	0	0	0	8	>64	>64	Yes	?
S.H. ..	,,	0	N.D.	N.D.	N.D.	0	8	32	128	,,	Yes
I.G.V. ..	,,	0	N.D.	0	0	0	16	>64	640	,,	?
U.J.D.R. ..	,,	0	0	0	0	0	4	64	128	,,	No
M.J.R. ..	,,	0	+	+	+	+	<4	8	120	,,	Yes
I.E.K.M. ..	,,	0	0	N.D.	0	0	N.D.	>64	64	N.D.	No
D.P.S. ..	,,	0	0	0	0	0	8	>64	120	Yes	,,
W.S.V. ..	,,	Moderate cold	0	0	0	0	<4	8	32	,,	Yes
S.V. ..	,,	0	0	0	0	+	4	>64	640	,,	?
D.C. ..	,,	0	0	0	0	0	<4	64	256	,,	,,
R.F.M. ..	$10^{3.2}TCD_{50}$	±	0	0	0	0	4	32	256	,,	,,
L.P. ..	,,	0	0	0	0	0	8	8	16	No	No
F.R. ..	,,	0	0	+	0	+	<4	64	640	Yes	Yes
T.N.W.B.	,,	±	+	+	+	0	8	32	128	,,	,,
J.H. ..	,,	0	0	0	0	0	12	≥64	1,024	,,	?
A.T. ..	,,	0	0	0	0	0	32	64	640	No	,,
R.M.M. ..	,,	0	0	0	0	0	≥64	≥64	256	,,	No
A.B. ..	,,	0	0	0	0	0	12	32	64	,,	,,
A.Ba. ..	,,	±	+	0	+	+	8	16	N.D.	,,	N.D.
J.W.S. ..	$10^{2.6}TCD_{50}$	0	0	0	0	0	<4	120	200	Yes	No
J.M.S. ..	,,	0	0	0	0	0	8	32	64	,,	,,
J.D. ..	,,	0	0	0	0	0	<4	64	256	,,	Yes
M.H. ..	,,	0	N.D.	0	0	0	<4	12	64	,,	,,
K.M.G. ..	,,	0	0	0	0	0	<4	120	120	,,	No
R.G. ..	,,	0	0	0	0	0	4	64	120	,,	,,
M.M.H. ..	,,	0	0	0	0	0	4	64	1,024	,,	Yes
H.A.M. ..	,,	0	0	0	0	0†	64	256	256	,,	No
S.V.S. ..	,,	0	0	0	0	0	16	100	120	,,	,,
Totals ..		1/28‡	5/28							23/27	11/27

N.D. = Not done. ± = Mild upper respiratory tract symptoms.
* Sera taken before vaccination, before challenge, and two weeks after challenge.
† Herpes simplex virus was isolated from this volunteer on days 4 and 5.
‡ Numerator denotes number of volunteers with colds, virus isolations, or antibody rises; denominator the number challenged.

TABLE IV.—*Results of Challenge with H.G.P.-like Virus (P.K.) in Unvaccinated Volunteers*

Volunteer	Challenge Dose	Cold or Symptoms	Virus (P.K.) Isolations on Day				Reciprocal H.G.P. Antibody Titre in Sera*		Fourfold H.G.P. Antibody Rise. Post-challenge
			2	3	4	5	1st	2nd	
J.M.K.	$10^{1.9}TCD_{50}$	0	0	0	0	0	<4	<4	No
P.J.K.	,,	Mild cold	+	+	0	0	<4	256	Yes
L.C.	,,	,, ,,	+	+	+	0	4	32	,,
S.M.	,,	0	+	+	+	0	4	32	,,
J.K.F.	,,	0	N.D.	N.D.	0	0	16	16	No
M.W.	,,	0	0	0	N.D.	0	16	32	,,
M.P.S.	$10^{3.5}TCD_{50}$	Mild cold	0	0	0	0	≤4	24	Yes
M.C.T.	,,	,, ,,	+	+	0	0	≤4	64	,,
P.E.W.	,,	,, ,,	+	0	0	+	≤4	256	,,
M.V.B.	,,	,, ,,	+	+	0	0	4	640	,,
P.B.D.	,,	,, ,,	+	+	+	0	12	256	,,
M.F.	,,	±	+	+	+	+	≤4	32	,,
R.B.R.	,,	Mild cold	+	+	0	0	8	64	,,
B.R.	,,	0	+	+	0	0	20	128	,,
R.W.W.	,,	0	0	0	0	+	≤4	≤4	No
B.W.	,,	0	0	0	0	0	32	32	,,
B.R.E.	,,	Mild cold	0	0	0	0	≤4	≤4	,,
R.T.S.	,,	0	0	0	0	0	32	140	Yes
E.B.	$10^{2.5}TCD_{50}$	0	0	0	+	0	<4	16	,,
J.C.	,,	Moderate cold	+	+	0	0	<4	4	No
M.N.	,,	,, ,,	+	+	+	+	<4	8	Yes
L.M.M.	,,	0	0	0	0	0	N.D.	N.D.	N.D.
K.J.B.	,,	0	0	0	0	0	<4	16	Yes
Totals		11/23	14/23						15/22

* Sera collected before challenge and two weeks after challenge.

challenge seven of them had laboratory evidence of infection and four developed colds. Of 10 unvaccinated volunteers receiving the same dose of challenge virus, five had laboratory evidence of infection and six had colds. As in the study by Mufson *et al.*, most of the illnesses occurred in volunteers who had responded poorly to vaccination. The dose of challenge virus used by Mufson *et al.*, 10^4 TCD_{50}, was greater than that used in our present experiments, but nevertheless we used more virus than probably initiates most naturally acquired infections (Buckland and Tyrrell, 1965). An earlier report by Price (1957) mentioned experiments which suggested that formalin-inactivated E.C.H.O. 28 vaccine would protect against illness in a naturally occurring E.C.H.O. 28 epidemic.

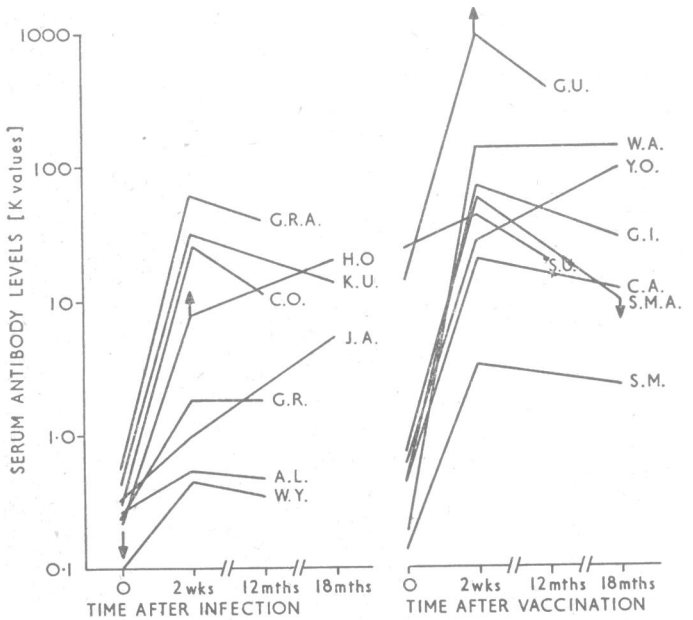

FIG. 2.—Persistence of antibody in volunteers either infected or vaccinated with H.G.P. or P.K. virus.

Our results presented in this paper have shown that it is possible to make a rhinovirus vaccine which will protect against colds due to experimental infection with homologous, but not heterologous, virus. Vaccination did not prevent subclinical infection, and this might be of importance, as such infections could maintain antibody at a high level. The vaccine induced H.G.P. antibody responses in virtually all volunteers, even in those who had no detectable pre-existing antibody. It was thus a more potent antigen than the P.K. vaccine used in our previous experiments, and this was the probable reason for our success on this occasion. As M rhinoviruses seem to be better antigens than H rhinoviruses it is important to show that it is possible to produce equally potent antigens with viruses of the latter type. Further work is also needed to show whether a polyvalent vaccine can be made, using both M and H strain rhinoviruses.

Results of experiments with the adjuvants Drakeol-Arlacel and aluminium phosphate have not shown any enhancement of antibody levels. It is, however, possible that antigenicity was being destroyed in the Drakeol-Arlacel, and it is still worth experimenting with modified mineral oil or other adjuvants.

Although aluminium phosphate does not show promise as an adjuvant for rhinoviruses, adsorption and elution could be useful for concentrating and purifying the virus components to be used in a polyvalent vaccine, as has already been done with polioviruses (Fantes, 1962).

Summary

A vaccine has been prepared against a strain of rhinovirus, H.G.P. ; this vaccine protects volunteers from clinical infection with homologous virus P.K. One out of 28 vaccinated volunteers had a cold compared with 11 out of 23 unvaccinated volunteers. The vaccine did not protect against challenge with heterologous virus E.C.H.O. 28. In addition, it was shown that antibody resulting from vaccination persisted for 12 to 18 months as well as antibody resulting from experimental infection.

TABLE V.—*Result of Challenge with E.C.H.O. 28 Virus in Vaccinated Volunteers*

Volunteer	Challenge Dose	Cold or Symptoms	Virus (E.C.H.O. 28) Isolation on Day				Reciprocal of H.G.P. Antibody Titre in Sera			Reciprocal of E.C.H.O. 28 Antibody Titre in Sera*			Fourfold Antibody Rises to			
													H.G.P.		E.C.H.O. 28	
			2	3	4	5	1st	2nd	3rd	1st	2nd	3rd	Post-Vac.	Post-chall.	Post-vac.	Post-chall.
J.A.T. ..	$10^{1.2}TCD_{50}$	Mild cold	+	+	0	0	< 4	256	256		< 4	32	Yes	No	No	Yes
M.B.T. ..	,,	0	0	+	+	0	< 4	32	32		< 4	64	,,	,,	,,	,,
K.M.B.	,,	Mild cold	+	0	0	0	< 4	256	200	8	8	256	,,	,,	,,	,,
B.G.H. ..	,,	0	+	+	0	0	8	150	150		< 4	32	,,	,,	,,	,,
H.P.B. ..	,,	±	+	0	0	0	32	64	150	< 4	< 4	32	No	,,	,,	,,
R.H. ..	,,	Mild cold	+	+	+	0	< 4	8	8		< 4	< 4	Yes	,,	,,	No
W.M.N.	,,	0	0	0	0	0	8	> 256	600	4	4	4	,,	,,	,,	,,
R.E.D.	,,	0	0	0	0	0	< 4	64	256	< 4	< 4	4	,,	,,	,,	,,
N.B. ..	,,	0	+	+	0	+	< 4	32	32		< 4	16	,,	,,	,,	Yes
V.M.C. ..	,,	Severe cold	+	+	+	+	< 4	200	256		< 4	16	,,	,,	,,	,,
C.I.H. ..	,,	Moderate ,,	+	+	+	0	< 4	> 256	1,024		< 4	16	,,	,,	,,	,,
D.L.J. ..	,,	0	0	0	0	+	< 4	32	32	16	16	256	,,	,,	,,	,,
B.P.P. ..	,,	Moderate cold	+	+	+	+	< 4	12	32		< 4	< 4	,,	,,	,,	,,
Totals		6/13	11/13										12/13	0/13	0/13	9/13

* Sera collected before vaccination, before challenge, and two weeks after challenge.

TABLE VI.—*Result of Challenge with E.C.H.O. 28 Virus in Unvaccinated Volunteers*

Volunteer	Challenge Dose	Cold or Symptoms	Virus (E.C.H.O. 28) Isolation on Days				Reciprocal of E.C.H.O. 28 Antibody Titre in Sera*		Fourfold Antibody Rise. Post-challenge
			2	3	4	5	1st	2nd	
A.R.J.A. ..	$10^{1.2}TCD_{50}$	Moderate cold	+	+	+	+	< 4	64	Yes
J.A.S. ..	,,	0	+	+	+	0	< 4	16	,,
J.W. ..	,,	0	+	+	0	0	< 4	< 4	No
P.M.L. ..	,,	0	0	0	0	0	< 4	< 4	,,
A.R.S. ..	,,	0	0	0	0	0	< 4	8	Yes
A.B.T. ..	,,	± (late)	0	0	+	+	< 4	< 4	No
S.C.D. ..	,,	± (late)	+	+	+	+	< 4	64	Yes
C.A.H. ..	,,	0	0	0	+	0	< 4	16	,,
H.S.S. ..	,,	0	+	0	+	+	4	N.D.	N.D.
I.S. ..	,,	Mild cold	+	+	+	0	< 4	4	No
	Totals	2/10	8/10						5/9

* Sera collected before challenge and two weeks after challenge.

Experiments on the use of mineral oil adjuvants and aluminium phosphate as an adjuvant showed little promise, although aluminium phosphate may be of value for concentrating and purifying antigen.

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Treatment of Acute Haematogenous Osteitis in Children Assessed in a Consecutive Series of Selected Cases

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Widespread lack of agreement about the correct treatment of a relatively common disease may be due to comparable lack of agreement about the clinical definitions and the standards of comparison which should be used in studying the problem. Disagreement about the correct treatment of acute haematogenous osteitis in children is both widespread and chronic. Its most recent overt manifestation was in the correspondence which followed the article by Harris (1962) in which he advocated early surgical drainage, including drilling to "decompress" the bone, as the one sure way of preventing the complication of a "chronic infection with a discharging sinus or obvious sequestrum formation." In the subsequent correspondence, equally strong conviction appeared to support every variety of advice, from the statement that "the only rational procedure is to 'deroof' the cavity and scoop out the debris" (Subrahmanyan, 1962), through a variety of equally emphatic statements concerning the proper place of antibiotics, surgical drainage, aspiration, and splintage, to the pronouncement by Pappworth (1962) that "the treatment of acute osteomyelitis is not surgery but the correct use of antibiotics."

The seriousness of the situation brought about by this state of confusion and lack of clear purpose is illustrated by the startling incidence of complications (as defined above) reported during the past few years—31% by Harris (1962), 28% by Mann (1963), and 31% of the cases treated by operative decompression by Gilmour (1962). The declared purpose of Mann's (1963) paper was to oppose early surgical drainage and to support the view that "the proper treatment of acute osteitis depends upon early diagnosis and prompt initiation of full treatment, including rest, splintage, and correct antibiotic therapy" (in that order).

The lack of agreement about clinical definitions and standards of comparison, which has led to such widespread disagreement about treatment, is rather less obvious, perhaps, but can be illustrated by reference to the last three papers quoted. Harris (1962) implied that there was some virtue in the fact that his 84 patients were "unselected." But the truth is that, in such a disease as this, failure to select cases for study implies failure to allow for the many definable factors which may affect the outcome and which "all summate to make each case unique" (Mann, 1963). "Unselected" cases of this disease cannot usefully be compared with each other. Moreover, it is strange to find that of the five cases which Harris describes in a paper whose title referred to the "early stages of acute osteomyelitis," one was admitted 28 days after the onset, in another the essential surgical intervention was delayed for 17 days, and in a third no effective antibiotic treatment was given for the first 19 days. The clinical definitions used by Mann (1963) are equally open to question. Of the 59 cases which he included, the clinical diagnosis was supported by radiological evidence "in most patients"—but by no confirmatory evidence in the remainder. Purely clinical evidence is, of course, all that should be available, or necessary, for the clinical purpose of initiating treatment: but such evidence alone is inadequate for the scientific purpose of determining the results of treatment (Trueta and Morgan, 1954). Reliance upon this sort of evidence may explain Mann's (1963) statement that "some are treated satisfactorily at home." We do not know of any such case in which the diagnosis was based upon acceptable evidence: and one need look no further than his own Case 1 to see the disastrous consequences which may result from a policy based on such a statement. But our main criticism concerns his sweeping condemnation of all studies of this disease which "tend to be statistical," on the ground that no group of cases is "homogeneous." This seems all the more surprising since he listed a number of factors likely to affect the outcome, which could (if properly defined) have been used to select a series of cases suitable for comparative studies. Gilmour (1962) went so far as to stress the importance of dividing cases into three grades of severity (mild, moderate, and severe) before analysing the results of treatment in any series, but did not define his grades of severity or apply his advice to the analysis of his own series. He also dismissed the question of delay in admission to hospital as having no effect upon the outcome.

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