A comparison is made in this paper of the response to a combined diphtheria-pertussis-tetanus-polio vaccine, to commercial polio vaccine, and to commercial DPT. The response to the polio vaccine was found significantly enhanced in the combined vaccine.

STUDIES ON A COMBINED DIPHTHERIA-PERTUSSIS-TETANUS-POLIOMYELITIS VACCINE

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THE PRACTICE of using combined diphtheria, pertussis, and tetanus antigens (DPT) is well established, and the efficiency of DPT in pediatric practice has been discussed by Ipsen.[1] Trivalent poliomyelitis vaccine prepared from virus inactivated with formalin[2] has been demonstrated to be effective in reducing the paralytic effect of acute poliomyelitis[3,4] and to evoke a significant antibody response in infants.[5] The possibility of incorporating the poliovirus antigen into DPT has aroused considerable interest. The response of infants to poliomyelitis vaccine and DPT injected simultaneously into separate sites and to poliomyelitis vaccine mixed in a syringe with DPT just before injection has been reported by Batson, et al.[6,7] Kendrick and Brown[8] and Levine[9] have studied the antigenicity of such mixtures in animals. Barrett, et al.,[10] recently published the results of clinical studies of a combined DPT-poliomyelitis vaccine. This report describes the response of mice, monkeys and guinea pigs to "Tetravax," a combined DPT-poliomyelitis vaccine.

Materials and Methods

Preparation of Vaccines—The poliomyelitis vaccines used in all preparations were bulk samples taken from production lots of commercial poliomyelitis vaccine that later met all the minimum requirements and were released for distribution by the Division of Biologics Standards of the National Institutes of Health (NIH). The diphtheria and tetanus toxoids were formalin-treated, purified concentrates prepared without preservative. Bordetella pertussis cells were grown in the liquid media of Verwey, et al.,[11] and killed with 1:40,000 benzethonium chloride. Because of the deterioration in antigenicity of poliomyelitis vaccines containing certain preservatives,[12] benzethonium chloride at a final concentration of 1:40,000 was used as a preservative in all vaccines. The combined diphtheria-pertussis-tetanus and poliomyelitis vaccine (DPT-P) preparations were made by mixing poliomyelitis vaccine with the concentrated toxoids and pertussis vaccine. The formula was composed so that the diphtheria-pertussis-

tetanus components were contained in 0.1 ml and combined with 0.9 ml of poliomyelitis vaccine to yield an immunizing dose of 1 ml. Enough potassium alum was added to adsorb the antigens from solution and the reaction was adjusted to pH 7.0. Control vaccines of diphtheria-pertussis-tetanus were prepared from the same reagents used for each lot of the quadruple vaccine.

Tests for pertussis potency were performed by the intraperitoneal injection of mice with graded dilutions of the antigen and challenge after 14 days by the intracerebral injection of a mouse-virulent strain of B. pertussis.[13,14]

Tests for diphtheria and tetanus potency were performed according to recommendations of the NIH.[15,16] Guinea pigs were bled from four to six weeks after subcutaneous injection of the antigens. Equal portions of serum from all animals surviving the immunization period were pooled. The titer of the pooled serum was determined by mixing with test toxin and injecting the mixture into guinea pigs. The test dose of the toxins was determined by neutralization with the appropriate NIH standard antitoxin.

Tests for polio potency were done by comparison of the antibody levels produced in monkeys by the vaccine under test with the antibody levels of reference serums distributed by the NIH.[17] Groups of 12 rhesus or cynomolgus monkeys weighing from four to eight pounds were injected intramuscularly with three 1 ml doses of the vaccines at seven-day intervals. Blood samples were taken prior to vaccination and seven days after the last injection. Serum was separated and inactivated by heating at 56°C for 30 minutes. Antibody levels were determined by the serum-virus neutralization test essentially as described by Salk, et al.[18] The results are expressed as ratios of the titers of test serums to those of the reference serum.

Tests for freedom of toxicity were performed as recommended by the NIH.[13] Each of five Swiss mice, weighing 14-16 grams, was injected intraperitoneally with one-fifth the total human dose. The mice were weighed again after three and seven days. For a vaccine to be considered satisfactory the mice must all survive, not show a weight loss after three days, and show a normal weight gain after seven days.

Animal safety tests were performed using mice and guinea pigs as recommended by the NIH.[13] Each of three guinea pigs, weighing 300-400 grams, was injected intraperitoneally with the total human dose of the vaccine under test. Each of two white Swiss mice, weighing 17-21 grams, was injected intraperitoneally with 0.5 ml of the vaccine under test. All animals were observed for seven days. For a vaccine to be considered satisfactory, all the

Table 1—Potency Tests of Diphtheria and Tetanus Toxoids*

Lot No.	Diphtheria		Tetanus	
	DPT-P†	DPT‡	DPT-P	DPT
A	3§	–	5	–
B	4	4	8	7
C	4	4	5	7
D	3	3	8	8
E	4	4	8	5
F	2	3	6	8
G	4	4	4	3
H	2	–	2	–
I	2	2	5	4
J	2	–	5	–
K	4	–	>2	–

* 1.5 ml of vaccine was injected subcutaneously into nine or ten normal guinea pigs weighing 500 grams ± 10 per cent. The animals were bled after four weeks, and the serum pools were titrated for antitoxin by mixing with the appropriate test toxin and injecting the mixture into two guinea pigs.

† DPT-P—Combined diphtheria-pertussis-tetanus-poliomyelitis vaccine.

‡ DPT—Combined diphtheria-pertussis-tetanus vaccine.

§ Antitoxin units per ml. (NIH requirements: two units.)

animals must survive and must not show either significant symptoms or loss in body weight.

Results

Diphtheria and tetanus potency tests were performed simultaneously on several lots of DPT-P and their respective DPT control vaccines. The results of these tests are summarized in Table 1. All of the preparations met the NIH minimum requirements for both diphtheria and tetanus potency. The antitoxin responses elicited to both toxoids by the quadruple vaccine were equivalent to those produced by the triple vaccine. This indicates that poliomyelitis vaccine does not alter the antibody response in guinea pigs to either diphtheria or tetanus toxoid.

Simultaneous potency tests for pertussis were done on several lots of DPT-P, DPT, and the pertussis concentrates from which they were made. All of the preparations (Table 2) met the NIH minimum requirements for pertussis potency. The response to the pertussis component in the quadruple vaccine was not significantly different from the response of the pertussis component in either DPT or alone. Although there are some variations in the test results, it appears that in mice poliomyelitis does not interfere with the antibody response to pertussis vaccine.

The DPT-P preparations and their poliomyelitis vaccine components were assayed for polio potency in monkeys. The results are given in Table 3. With the exception of Lot A, all vaccines exceed the minimum requirements. The polio type responding best in each lot appears to run parallel in both DPT-P and poliomyelitis vaccine. The increased response of the quadruple vaccine as compared to its corresponding poliomyelitis vaccine is shown also in Table 3. In every instance, except the Type I components of Lots A and D, the DPT-P preparations gave a better response to poliovirus than the poliomyelitis vaccines alone. This increased response by the combined vaccine is highly significant ($P = \ll 0.001$). It is of interest that in Lot A where the Type III component of the poliomyelitis vaccine was poor, there appears to be no enhancement in the combined vaccine.

The results of tests for freedom of toxicity and animal safety are summarized in Table 4. With the exception of Lot A, all of the DPT-P and control DPT preparations were found to meet the minimum requirements of the NIH. Lot A was prepared from a pertussis concentrate subsequently shown to be highly toxic. Preliminary toxicity testing of pertussis concentrates eliminated this difficulty.

One lot of the quadruple vaccine (Lot C) was tested for diphtheria and tetanus potency initially and again after six and 12 months' storage at 2°-5°C. The results of these tests (Table 5)

Table 2—Summary of Pertussis Potency Tests*

Lot. No.	DPT-P†	DPT‡	Pertussis Concentrate
A	42.6§	—	22.4
B	21.5, 9.5	22.2	20.8
C	14.2	22.2	20.8
D	17.6	18.3	14.4
E	20.5	22.7	9.3
F	24.6, 10.3	18.4, 9.2	6.7, 11.2
G	22	12	28, 17, 23
H	15	—	14
I	7, 15.5, 12	10	11
J	40	—	58
K	10	—	17

* Mice were injected with graded doses of vaccine and 14 days later challenged intracranially with 100T organisms of B. pertussis (strain 18-323).
† DPT-P — Combined diphtheria-pertussis-tetanus-poliomyelitis vaccine.
‡ DPT—Combined diphtheria-pertussis-tetanus vaccine.
§ Protective units per total human dose. (NIH requirements: 3.0—36 units.)

Table 3—Summary of Potency Tests in Monkeys on Poliomyelitis Vaccine

Lot No.	Antigen	Type I		Type II		Type III	
A	DPT-P*		0.67†		1.52		0.08
	Poliomyelitis Vaccine		0.72		1.03		0.06
	Increase		(0.05)‡		0.49		0.02
B	DPT-P		0.81		4.92		0.43
	Poliomyelitis Vaccine		0.76		2.14		0.41
	Increase		0.05		2.78		0.02
C	DPT-P		0.71		4.28		1.52
	Poliomyelitis Vaccine		0.33		0.61		0.38
	Increase		0.38		3.67		1.14
D	DPT-P	0.31	0.29	1.74	1.63	1.86	1.41
	Poliomyelitis Vaccine	1.51	0.81	1.74	0.76	1.63	1.07
	Increase	(1.20)	(0.52)	0	0.87	0.23	0.34
E	DPT-P		0.54		2.46		1.23
	Poliomyelitis Vaccine		0.33		0.61		0.38
	Increase		0.21		1.85		0.85
F	DPT-P	1.41	1.07	2.14	4.28	4.00	2.14
	Poliomyelitis Vaccine	0.93	0.35	1.07	1.00	0.62	0.31
	Increase	0.48	0.72	1.07	3.28	3.38	1.83
G	DPT-P		1.15		2.46		1.74
	Poliomyelitis Vaccine		0.54		0.76		0.76
	Increase		0.61		1.70		0.98
I	DPT-P		1.87		5.65		4.29
	Poliomyelitis Vaccine		0.54		0.76		0.76
	Increase		1.33		4.89		3.53
J	DPT-P		1.41		5.66		4.59
	Poliomyelitis Vaccine		1.00		2.46		2.46
	Increase		0.41		3.20		2.13
K	DPT-P	1.23	4.00	3.24	6.06	4.28	13.00
	Poliomyelitis Vaccine	1.41	1.41	1.51	1.51	2.30	2.30
	Increase	(0.18)	2.59	1.73	4.55	1.98	10.70

* DPT-P—Combined diphtheria-pertussis-tetanus-poliomyelitis vaccine.
† Ratio of test serum to NIH reference serum. (NIH requirements: Type I, 0.29; Type II, 0.25; and Type III, 0.16.)
‡ Brackets around figures indicate a decrease.

Table 4—Tests for Freedom of Toxicity* and Animal Safety†

Lot No.	Freedom of Toxicity		Animal Safety	
	DPT-P‡	DPT§	DPT-P	DPT
A	U¶	–	U	–
B	S	S	S	S
C	S	S	S	S
D	S	S	S	S
E	S	S	S	S
F	S	S	S	S
G	S	S	S	S
H	S	–	S	–
I	S	S	S	S
J	S	–	S	–
K	S	–	S	–

* Each of five mice, weighing 14–16 gm, was injected intraperitoneally with one-fifth the total human dose. For a vaccine to be considered satisfactory, all the mice must survive, not show a weight loss after three days, and show a normal weight gain after seven days.
† Each of three guinea pigs (300–400 gm) was injected intraperitoneally (i.p.) with the total human dose of vaccine. Each of three mice (17–21 gm) was injected i.p. with one-half ml of vaccine. For a vaccine to be considered satisfactory, all the animals must have survived and not show significant symptoms for seven days.
‡ DPT-P — Combined diphtheria-pertussis-tetanus-poliomyelitis vaccine.
§ DPT—Combined diphtheria-pertussis-tetanus vaccine.
¶ U—Unsatisfactory. S—Satisfactory.

show that the toxoid components of DPT-P are stable for at least 12 months when held at 2°-5°C.

Samples of four lots of DPT-P and their control DPT components were tested for pertussis potency after storage at 2°-5°C for periods up to 12 months. The results summarized in Table 6 show that in the quadruple vaccine the pertussis potency has not changed significantly. Although there are some discrepancies in the testing, we may conclude that the pertussis component is stable for at least from eight to 12 months when held at 2°-5°C.

Three lots of DPT-P and the poliomyelitis vaccines from which they were prepared were stored at 2°-5°C. The vaccines were potency tested in monkeys at the time of their preparation and again approximately one year later. The results summarized in Table 7 show that all three lots still exceeded the minimum requirements. Although the variability of the monkey potency test makes statistically valid conclusions impossible, it appears that with the possible exception of Type III, the polio components are stable when held at 2°-5°C for periods up to one year.

Discussion

The most obvious advantage in the use of multiple antigens is the fewer injections required. Also the protection against a disease of low incidence such as tetanus becomes practical. Another advantage may be the synergistic effects reported by Greenberg and Fleming,[19] who demonstrated that the addition of H. pertussis vaccine to diphtheria and tetanus toxoids enhances the activities of both antigens.

There also are certain problems in the use of combined antigens. These include difficulties in formulation, incompatibilities, and the proper timing of injections so that the several antigens produce at least as good response to the individual antigens as if they were used separately. It is important that

Table 5—Stability* of Diphtheria and Tetanus Toxoids in DPT-P†

Storage Period	Diphtheria Toxoid	Tetanus Toxoid
Original	4‡	5
6 months	4	4
1 year	4	4

* DPT-P—Lot C was held at 2°–5°C and tested periodically for diphtheria and tetanus potency. One and one-half ml of vaccine was injected subcutaneously into nine or ten normal guinea pigs weighing 500 grams ± 10 per cent. The animals were bled after four weeks, and the serum pools were titrated for antitoxin by mixing with the appropriate test toxin and injecting the mixture into two guinea pigs.
† DPT-P — Combined diphtheria-pertussis-tetanus-poliomyelitis vaccine.
‡ Antitoxin units/ml (NIH requirements: two units.)

Table 6—Stability* of B. pertussis Vaccine in DPT-P† and DPT‡

Lot No.	Storage Period	DPT-P	DPT
B	Original	15.5§	22.2
	8 months	14.0	—
	12 months	—	14.5
C	Original	14.2	22.2
	6 months	6.0	—
	8 months	11.0	—
	12 months	9.0	14.5
D	Original	17.6	18.3
	8 months	20.0	—
	12 months	—	10.5
F	Original	17.4	13.8
	5 months	9.0	—

* Vaccine stored at 2°–5°C were tested for pertussis potency in mice.
† DPT-P — Combined diphtheria-pertussis-tetanus-poliomyelitis vaccine.
‡ DPT—Combined diphtheria-pertussis-tetanus vaccine.
§ Protective units per total human dose. (NIH requirements: 8.0—36 units.)

multiple antigens cause no untoward reactions; nor when mixed, should one constituent lessen the antigenic potency of the others. These problems have been overcome with the quadruple vaccine.

Kendrick and Brown[8] reported a possible depression of the serologic response of guinea pigs to diphtheria and tetanus toxoids and to poliomyelitis vaccine when these antigens were administered together in DPT-P. Levine[9] studied the effect in guinea pigs of mixtures of diphtheria toxoid and poliomyelitis vaccine and found no significant effect on the response of the animals to the toxoid due to the vaccine. We found no suggestion of a depression of the antigenic response of guinea pigs to either diphtheria or tetanus toxoids. The response of poliomyelitis vaccine in guinea pigs was not followed.

Kendrick[8] also reported that all antibody levels appeared to be somewhat higher in monkeys following injection of the combined products than following poliomyelitis vaccine alone. Our results indicate that this increased response of monkeys to poliomyelitis following injection of the combined product is highly significant. Although it may be dangerous to generalize on the basis of results in one animal species, one is always hopeful that the increased response will be the case in human beings. The reports of Barrett, et al.,[10] and Batson, et al.,[6,7] have indicated no evidence of any interference between the antigens when injected into human beings.

The proposed schedule for the use of the quadruple vaccine will be 1 ml each month for three months followed by a 1-ml booster dose from six to 12 months later. In contrast, the recommended schedule for poliomyelitis vaccine is two injections of 1 ml each spaced four weeks apart, and a 1-ml booster dose from six to 12 months after the second injection. The proposed schedule for the quadruple vaccine will insure that the patient receives 2.7 ml of the poliomyelitis vaccine component during the first three months of immunization rather than the usual 2 ml. and that the total immunizing dose will be 3.6 ml rather than the usual 3 ml. The additional quantity of vaccine administered may be of importance in view of recent discussions regarding the antibody response to poliomyelitis vaccine.[20]

The combined diphtheria-pertussis-tetanus-poliomyelitis vaccine has undergone extensive clinical studies and the results will be reported elsewhere.

Summary

A combined diphtheria-pertussis-tetanus-poliomyelitis vaccine was prepared and compared with commercial diphtheria-pertussis-tetanus vaccine and with commercial poliomyelitis vaccine. The diphtheria. pertussis and tetanus components responded equally well in the triple

Table 7—Stability* of Poliomyelitis Vaccine in DPT-P†

Lot No.	Storage Period	DPT-P			Poliomyelitis Vaccine		
		Type I	Type II	Type III	Type I	Type II	Type III
C	10 weeks	0.71‡	4.28	1.52	0.33	0.61	0.38
	6 months	0.31	1.62	0.57	—	—	—
	8 months	0.20	0.66	0.43	—	—	—
	14.5 months	0.41	1.32	0.71	—	—	—
D	Original	0.31	1.74	1.86	1.51	1.74	1.63
	"	0.29	1.63	1.41	0.81	0.76	1.07
	12 months	0.57	2.14	0.76	0.62	2.00	0.76
F	Original	1.41	2.14	4.00	0.93	1.07	0.62
	"	1.07	4.28	2.14	0.35	1.00	0.31
	12 months	1.23	3.73	1.32	1.15	1.86	0.71

* Vaccines stored at 2°–5°C were tested in monkeys for polio potency.
† DPT-P—Combined diphtheria-pertussis-tetanus-poliomyelitis vaccine.
‡ Ratio of test sera/control sera. (NIH requirements: Type I, 0.29; Type II, 0.25; and Type III, 0.16.)

and quadruple vaccines. The response to poliomyelitis vaccine was enhanced significantly in the combined vaccine. The combined antigen was shown to be safe, free of toxicity, and stable at 2°-5°C for at least one year.

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The Conference of State and Provincial Public Health Laboratory Directors is accepting until June 1, 1960, nominations for the 1960 and ninth annual Kimble Methodology Research Award. The award of $1,000 and a silver plaque gives recognition to the application of scientific knowledge in the public health laboratory. Established by the Kimble Glass Company of Toledo, the award is presented at the annual meeting of the conference, one of the related organizations joining in the 88th Annual Meeting of the APHA in San Francisco, October 31-November 4, 1960.

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