specific response, it might be rendered significant through inhibition by specific antiserums as was demonstrated with influenza virus (Table I). Neutralizing antiserums, prepared in chickens with several strains of common cold agent thus far studied, have demonstrated more than one antigenic strain.

It would be premature to say that even one common cold agent has been adapted to or propagated in the tissues of the embryonated egg. The decline of cytological response with passage gives no support to this proposition. Further studies on optimal passage interval and on tissue susceptibility may provide a means of adapting such agents to avian tissues and the process may be revealed through the cytological response in the AF of inoculated eggs. This would provide a technical advantage over the use of human volunteers for the detection of virus.

Summary. (1) Influenza and mumps viruses induced increased numbers of histiocytes in the allantoic fluids of embryonated eggs. The significance of this response was enhanced by coincident hemagglutinin production and by an interference effect on both responses by specific antiserums. (2) Nasal washings from acute common cold (afebrile rhinitis) patients engendered increased numbers of histiocytes in the allantoic fluid of embryonated eggs. The agent(s) responsible for this cytological response were thermolabile, were not inhibited by penicillin and streptomycin, and produced no detectable growth in bacteriological media. The agent(s) were not demonstrable in nasal washings collected from the same patients during convalescence. (3) Nasal washings from cases of acute allergic rhinitis did not induce increased numbers of histiocytes in the allantoic fluid of inoculated eggs.

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Inhibition by Aminopyrine of Adrenocortical Activation Caused by Pyrogenic Reaction.* (22291)

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Like a number of other stressful stimuli, typhoid vaccine has been shown to cause stimulation of the pituitary-adrenal axis in rats (1). In human subjects, Arendshorst and Falls(2) showed the occurrence of eosinopenia following typhoid vaccine administration, and Rosen(3) and Conn, *et al.*(4) demonstrated increases in urinary 17-ketosteroid and "corticoid" excretion after injection of

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this material. Bliss and his co-workers(5) found that milder febrile stimuli, produced by bacterial pyrogen (Piromen®), caused moderate rises in the levels of plasma 17-OH-corticosteroids.

It seemed that this adrenocortical response to a stimulus might afford a means of studying some of the factors involved in activation of the pituitary-adrenal system. In this study, an attempt was made to learn whether the adrenocortical stimulation depended entirely on the febrile response to typhoid vaccine, or could be produced in the absence of fever. This approach appeared to be of particular interest in view of the studies of Bradley, *et al.*(6), who found that an antipyretic agent inhibited the febrile response to typhoid vaccine, but did not prevent certain renal hemodynamic changes characteristic of the pyrogenic reaction.

Materials and methods. The patients included in this study were 17 adult men and women, in good general health, who were admitted to the Institute of Ophthalmology of the Presbyterian Hospital for treatment of various inflammatory disorders of the eye. Typhoid vaccine (obtained from the Department of Health, City of New York—1 ml contains 1,000 million killed *S. typhosa* organisms, 250 million killed *S. paratyphi* A, and 250 million killed *S. paratyphi* B organisms) was diluted with saline and injected in a standardized manner. 5 to 10 million *S. typhosa* organisms (plus 1.25 to 2.5 million of both *S. paratyphi* A and B) were administered in a single intravenous injection, followed in 2 hours by a similar dose. Rectal temperatures were taken at hourly intervals. Adrenocortical response was assessed by measuring changes in plasma 17-OH-corticosteroid levels, determined according to the method of Silber and Porter(7) as previously described(8). Control blood specimens were obtained, and additional specimens were drawn at intervals following administration of typhoid vaccine (Table I). No rise in plasma 17-OH-corticosteroid level was regarded as significant unless values exceeded the upper limit of normal. Normal limits in this laboratory are 4-28 μg per 100 ml plasma.

TABLE I. Effect of Intravenous Typhoid Vaccine on Levels of Plasma 17-OH-Corticosteroids. Time in hr after 2nd vaccine injection.

Patient	Max temp., °F	Plasma 17-OH-corticosteroids, γ % Control	2 hr	4 hr	6 hr
1	103.8	18	43	34	
	103.8	28		42	40
2	104.8	15	59	30	
	102.4	13	32		
3	103.8	17	40	35	16
	103.4	22		32	
4	102.6	20	40		
5	102.8	13		30	
6	105.6	14	53	36	
7	104.2	8	28	29	
	105.6	13	46	34	16
8	103.8	7	32		
9	103.6	17	36		42
	104.0	19	37		13
	104.8	18		35	
10	103.6	17		35	
	102.6	24			24
11	104.0	20	43	45	
12	102.6	18	33	22	
	102.4	14	38		
13	104.4	17	36		
	103.4	26		27	
14	102.6	16	36		
15	102.4	14	29	17	

In 7 of the patients, the anti-pyretic, aminopyrine was given over a 24-hour period in a dose of 0.6 g every 4 hours. Immediately following the last dose of aminopyrine, typhoid vaccine was administered according to the schedule outlined above, with blood samples being obtained in the same manner.

Results. 1. *Effect of typhoid vaccine alone.* In 15 patients, typhoid therapy was given on 24 separate occasions. In all 24 instances, there was a sharp rise in temperature to 102.4-105.6°F, occurring within 2 to 5 hours after the second dose of vaccine. The control 17-OH-corticosteroid values fell within the normal range (Table I). In 22 of the 24 experiments, plasma 17-OH-corticosteroid levels rose, within 2 to 6 hours after the second dose, to values above the normal which ranged from 29 to 59 μg per 100 ml plasma. These levels were comparable to those attained in normal subjects after intravenous infusion of 25 mg ACTH(9). In 4 of the patients, in whom studies were made of diurnal variations in levels of circulating 17-OH-

corticosteroids, such abnormally high values were not found. In these patients, corticosteroid levels fluctuated within the normal range. In 4 additional instances, typhoid vaccine failed to produce a rise in temperature above 101°F, and the febrile response was delayed. In these cases, plasma corticosteroid levels did not rise above the upper limit of normal.

2. *Effect of aminopyrine.* In all 7 patients treated with aminopyrine, injection of typhoid vaccine failed to cause pyrexia above 100.4°F. In 6 of the patients, there were no significant rises in plasma 17-OH-corticosteroid levels, values remaining within normal limits (Table II). In the seventh (patient #8, Table II), plasma 17-OH-corticosteroid levels rose from 20 to 28 μg per 100 ml, the upper limit of normal. It was noteworthy that in all 7 subjects, constitutional symptoms (malaise, weakness, nausea, chilly sensations) occurred despite the absence of fever. Failure of plasma 17-OH-corticosteroid levels to rise in the aminopyrine-treated subjects did not seem attributable to refractoriness to the pyrogenic effect of the vaccine. As can be seen in Fig. 1, repeat administration of comparable doses of vaccine in the 3 patients restudied without aminopyrine, again caused rises in temperature, associated with an increase in plasma 17-OH-corticosteroid values.

3. *Effect of central nervous system depressants.* (a) Barbiturate. In a single subject, 1 g of Amobarbital sodium (Na amytal) was administered in divided doses before and during standard vaccine injection. The temperature rose to 105.6°F within 3 hours after the second dose of vaccine. Plasma 17-OH-corticosteroid rise was not inhibited, rising from a control level of 13, to 43 μg per 100 ml.

(b) 10-(γ-dimethylaminopropyl)-2-chlorophenothiazine (Chlorpromazine). This broadly-acting agent, chosen because of its depressant effect on hypothalamic centers(10), was administered to 8 patients in doses up to 250 mg, before and during typhoid vaccine therapy. In 6 instances, plasma 17-OH-corticosteroid rises occurred in a manner comparable to that shown in Table I. In 2 cases, corticosteroid rises did not occur, but in both instances, febrile response was delayed and was of only moderate degree.

4. *Controls.* (a) To rule out the possibility that the aminopyrine suppression of plasma corticosteroid rise could be due to blockade of adrenocortical response to endogenous ACTH, a single normal male was treated for 24 hours with aminopyrine (0.6 g every 4 hours), and then subjected to a standardized ACTH test. Plasma 17-OH-corticosteroid levels rose from 10 to 45 μg per 100 ml, a response well within the limits of normal(9). (b) To exclude a direct inhibitory effect of aminopyrine on pituitary release of ACTH, a normal subject was given an insulin tolerance test (0.15 unit of standard insulin per kilogram body weight administered intravenously). Plasma 17-OH-corticosteroid levels rose from 20 to 28 μg per 100 ml(5). After treatment for 24 hours with aminopyrine, 3.6 g, repeat insulin administration was again associated with a rise in plasma corticosteroid value, from 6 to 30 μg per 100 ml. (On 2 different days, diurnal variation in plasma corticosteroid levels in this patient showed a definite fall in values.)

TABLE II. Effect of Aminopyrine on Plasma 17-OH-Corticosteroid Response to Intravenous Typhoid Vaccine. Time in hr after 2nd vaccine injection. (Patient numbers correspond to those in Table I.)

Patient	Max temp., °F	Plasma 17-OH-corticosteroids, γ % Control	2 hr	4 hr	6 hr
1	99.4	25	24		13
2	99.6	14	17		11
3	100.4	24	22	24	
8	99.6	20	28		
14	98.6	14	19		
16	99.0	27	27		
17	98.4	28	20		

Discussion. The rise of plasma 17-OH-corticosteroids to levels above the normal following typhoid vaccine injection confirms the fact that this agent is capable of producing adrenocortical activation in the human subject(2-5). Blockade of the febrile response to the vaccine by aminopyrine inhibits this plasma corticosteroid increase. The inference is that the fever *per se* is the essential factor in bringing about activation of the pituitary-adrenal system. Presumably, other

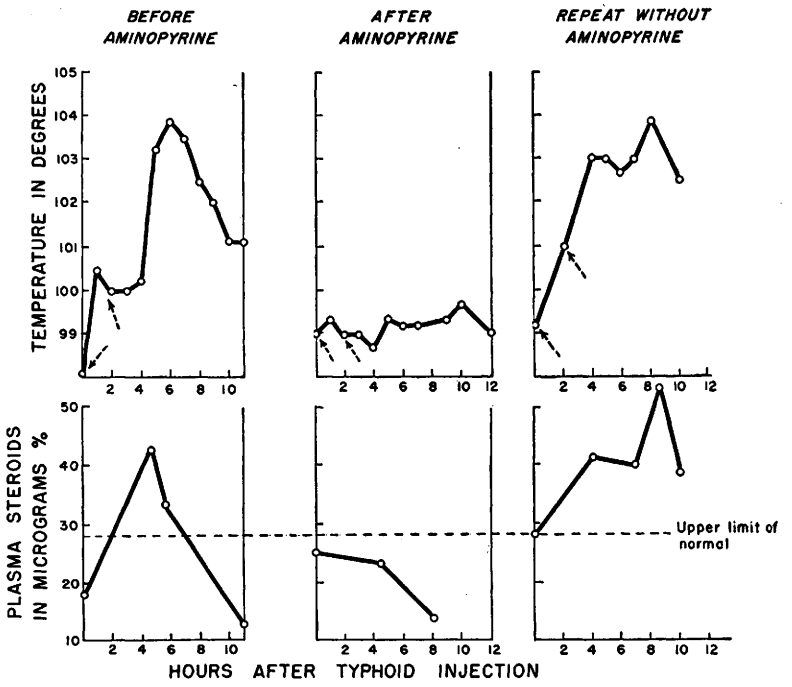

FIG. 1. Febrile and plasma 17-OH-corticosteroid response to intravenous typhoid vaccine injection (patient #1, Table I). The 3 series of vaccine injections were performed at intervals of 3 days. Arrows indicate times of injection of vaccine.

noxious effects of the vaccine which are not prevented by an antipyretic agent(6), are not effective in activating the adrenal cortex, as measured by this index of response. Furthermore, other central nervous system depressants, in the doses used, failed to inhibit plasma corticosteroid rises, unless the febrile response was also partially blocked.

The inhibitory effect of aminopyrine did not appear to act directly on the pituitary-adrenal system. The drug did not interfere with the adrenocortical response to administered ACTH, nor did it inhibit the pituitary-adrenal reaction to a non-febrile stimulus (insulin hypoglycemia).

Summary. Intravenous administration of typhoid vaccine to human subjects produced adrenocortical activation, as measured by increases in levels of circulating 17-OH-corticosteroids. Suppression of the pyrogenic effect of the vaccine by aminopyrine prevented adrenocortical response, without blocking certain other systemic reactions.

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