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## IMMUNOLOGIC STUDIES IN HYPERPYREXIA \*

(1935)

*Glaser* ✓

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Few immunologic studies have been made of patients treated with hyperpyrexia. Most workers have limited their investigations to chemical changes and have fairly well established that any alterations in the blood of patients undergoing hyperthermia are slight and transient.

Feinberg, Osborne and Afremow<sup>(1)</sup> noted a moderate increase (about ten per cent) in the erythrocyte count of asthmatic patients during the diathermy fever. They concluded, as did Mortimer<sup>(2)</sup> that this was a blood concentration effect. (The leucocyte count, however, in most cases showed a definite increase, sometimes as much as 100 per cent.) There was also a slight tendency towards acidosis. On the theory that allergy is a state of potential alkalosis they alkalinized a group of patients, but found that in spite of alkalinization diathermy still caused improvement. In five patients with positive skin tests intradermal injections with dilutions of the allergens showed no appreciable change after treatment. Quantitative determinations of the atopic reagents in these patients before, during and after diathermy treatment revealed no decided variations. Their experiments led them to believe that the mechanism producing relief from asthma after hyperpyrexia in-

volves a change neither in the acid-base balance of the blood nor in the skin sensitiveness of the patient to the allergen.

Paretic patients receiving eight to twelve treatments were observed daily during treatment and at intervals for a month after treatment by King and Cocke.<sup>(3)</sup> They reported no changes in erythrocyte or leucocyte counts. Since they did not test the blood at the height of temperature they missed the changes found by Feinberg and Osborne.

The blood picture in 97 paretics, each receiving a course of twelve treatments, one every other day, was negative according to Wilgus and Lurie.<sup>(4)</sup> (The Wassermann reaction was not once altered.) Frequently there was an immediate flattening of the Lange colloidal gold curve. Cell counts of the spinal fluid indicated marked improvement. Globulin was reduced in many cases.)

Tenney<sup>(5)</sup> made a study of blood chemistry changes, clotting factors, blood counts, viscosity and blood sedimentation rates of individuals in whom an artificial fever was produced by radio frequency current. (The chemical changes were of small importance. There was a slight increase in the red blood cell count, due, the author suggested, to dehydration and also to stimulation of the blood forming organs, as shown by the younger forms of erythrocytes. An increase in the total leucocyte count was observed, the maximum in-

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crease occurring nine hours after treatment, with a return to normal in 20 hours. The blood viscosity was not increased during the height of temperature where loss of body fluid was replaced by a large fluid intake. There was a definite increase in the platelet count.

x | Carpenter and Page<sup>(6)</sup> stated that with heat the rate of chemical reactions concerned with the development of immunity and with the general defense mechanism of the body against infective agents increases. |

Many of the experiments dealing with the effect of artificial fever in animals have been in rabbits in which experimental syphilis has been produced.

Schamberg and Rule<sup>(7)</sup> tested the effect of hyperpyrexia in rabbit syphilis. They were able to sterilize the infection after about nine hot water baths lasting 15 to 20 minutes each. There was an average rise of 4 degrees C. in the animal's temperature after immersion in a bath of 45 degrees C.

Out of 25 rabbits infected intratesticularly with *Treponema pallidum* and treated by radio frequency waves, Carpenter and Boak<sup>(8)</sup> reported 21 as failing to develop chancres when treatments were begun, four, five and seven days after injection. Five of these 21 developed nodules but the lesions disappeared when the exposure was intensified. One treated rabbit developed a chancre, while the testes of a second became enlarged, edematous and indurated. On further treatment they became normal. One rabbit died from overheating and one from an intercurrent infection. Eighteen control rabbits infected in a similar manner developed the typical lesions of experimental syphilis.

Hicks and Szymanowski<sup>(9)</sup> studied the effects of the high frequency current on the precipitin titer in rabbits. No change was observed after six hours exposure. No beneficial effects were observed on the course of pneumococcus and streptococcus infections in guinea pigs and mice.

In five rabbits immunized to *Bacillus typhosus* and subjected to hyperpyrexia (temperatures from 40.5 to 43.1 degrees C.) (Ecker and O'Neal<sup>(10)</sup> observed a depression of agglutinins during the time of fever but the antibody titer soon returned to normal.) Nine normal guinea pigs in which temperatures from 40 to 42.8 degrees C. were obtained showed a decrease in complement in all dur-

ing the first heating. Subsequent heatings either decreased it or increased it. In any case the complement was not completely destroyed.

Reimann<sup>(11)</sup> reviewed the literature on hyperpyrexia and reported experiments in which he showed that the increased viscosity of the plasma, due to increase of certain plasma proteins, which occurs during febrile infection, enhanced the specific agglutinative power of immune serum. This increase in agglutinative power caused by augmentation of viscosity he thought might be an important factor in the defense mechanism against infection. From his own experiments and those of other investigators he concluded that the fever induced by diathermy was not effective in causing an increase in either globulin or fibrinogen which would be marked enough to change the viscosity of the plasma. By varying the viscosity of immune serum by the addition of acacia he was able to show a much greater clumping of bacteria than when immune serum alone was used. It is uncertain whether fever in itself causes protein changes sufficient in amount to produce such changes in viscosity. It probably needs the stimulation or irritation of the globulin or fibronogen forming organs.

#### Experiments

The method used in producing artificial fever in these cases is that reported by Neymann and Osborne<sup>(12)</sup> and consists briefly in the conduction of high frequency currents through the body of the patient by means of special large electrodes, the source of the current being a low voltage high frequency apparatus.

A total of 378 determinations were made on 17 patients. These included nine cases of intractable asthma, seven of infectious arthritis and one of general paresis. Below is listed the number of tests of each type which were performed.

	No. of Determinations	No. of Cases
Total leucocyte counts.....	46	8
Erythrocyte counts .....	38	8
Differential leucocyte counts	46	8
Complement titer .....	58	13
Opsonic index .....	84	17
Phagocytic power of leucocytes .....	29	4
Agglutination .....	77	4

Collection of materials for testing:

Blood was drawn into a syringe from the arm vein under sterile conditions. One part

of the blood was discharged into a tube containing heparin or sodium citrate solution, and the rest into a dry sterile tube. For the blood count the ear or finger was pricked and the white and red cell counts and differential counts made in the usual way.

#### Methods

**Complement.** The amount of complement present in the human serum was determined by first removing the native hemolytic amboceptor for sheep erythrocytes. This was done by incubating the serum with sheep's washed red blood cells at 2 degrees C. for one hour. The tube containing the serum and cells was then put into a centrifuge tube containing cracked ice and the mixture centrifuged about two minutes to throw down the red cells. Since complement does not act at this low temperature none of it was used

up in the process of removing native hemolysins. The removal of the amboceptor, however, was found not to have any significant influence on the results. The serum was then diluted one to three, and amounts varying from 0.01 to 0.04 were put into small tubes by means of a 0.1 cc. pipette graduated in hundredths. To this were added 0.1 cc. of antishoop amboceptor, diluted 1:250, and 1 cc. of a one per cent suspension of sheep's washed red blood cells. Enough saline was then added to each tube to make the whole volume 2 cc. The tubes were incubated for 30 minutes in a 37 degree C. water bath. Readings were made at the end of that time and also after 18 to 24 hours in the icebox. Only the smallest amount of serum showing complete hemolysis is reported in the tables.

**Opsonic index.** The ordinary method for

TABLE 1.—*Immunologic Effects of Diathermy in Asthma*

Case No.		Opsonic Index	Complement*	Rectal Temperature
1	First treatment			
	Before	1.0	0.20	101.8
	Height of temp.	1.2	0.20	104.6
2	First treatment			
	Before	1.0	0.40**	102.0
	Height of temp.	1.0	0.40	105.4
	5 days after first treatment	1.0	0.35	
	3 days after second treatment	1.0	0.35	
3	First treatment			
	Before	1.0	0.20	99.7
	Height of temp.	1.0	0.20	104.8
	19 days after first treatment	1.0	0.15	
	Third treatment			
	Height of temp.	1.2	0.20	104.7
	24 hrs. after	1.6	0.20	
	Fourth treatment			
	Before	1.0	0.15	99.1
	4	Second treatment		
	Before	0.8		100.2
	Height of temp.	Sample lost		103.1
	2 hrs. after	0.9	0.10	102.6
5	First treatment			
	Before	1.2	0.25	100.2
	24 hrs. after	1.2	0.20	Temp. at height was 105.1
	Second treatment			
	Before	1.1	0.20	99.6
	24 hrs. after	1.1	0.20	Temp. at height was 102.1
6	First treatment			
	Before	1.0	0.25(3+)	100.5
	24 hrs. after	1.0	0.25(3+)	Temp. at height was 103.6
	Second treatment			
	Before	1.1	0.20	100.4
	Not possible to get sample after treatment			
7	First treatment			
	Before	1.0	0.20	100.2
	24 hrs. after	0.8	0.20	Temp. at height was 103.7
8	First treatment			
	Before	0.8	0.15	101.4
	Height of temp.	0.8	0.20	104.5
	Second treatment			
	Before	1.1	0.15	99.9
	Height of temp.	0.8		103.6
	24 hrs. after	1.3	0.15	
9	First treatment			
	Before	1.4	0.15	100.3
	Height of temp.	0.7*	0.15	104.1
	24 hrs. after	0.9		

\* Serum diluted 1:3.

\*\* Serum diluted 1:5.

TABLE 2.—Immunologic Effects of Diathermy in Arthritis and General Paresis

Case No.		Opsonic Index	Complement	Red Cell Count in Millions	White Cell Count	*** Polys.	L.	E.	Tr.	M.	B.
10	First treatment										
	Before	1.0	.....	....	5500	54	44	1	1	0	0
	Height of temp.	1.2	0.10	....	9700	79	18	2	1	0	0
	24 hrs. after	0.9	0.30	....	9300	78	18	1	2	1	0
	Fourth treatment										
	Before	0.8	0.80	3.5	5200	63	35	1	0	0	1
	Height of temp.	0.8	0.30	4.5	14000	72	26	0	0	1	1
	24 hrs. after	0.6	0.30	4.8	7400	60	38	2	0	0	0
	Eighth treatment										
	Before	1.0	0.4(3+)	4.0	5400	56	42	1	1	0	0
	Height of temp.	0.9	0.4(3+)	4.7	17100	78	20	0	2	0	0
	24 hrs. after	0.7	0.4	5.1	5700	62	37	1	0	0	0
11	Fourth treatment										
	Before	1.0	0.30	4.3	8700	73	25	0	1	1	0
	Height of temp.	1.6	0.30	5.9	12800	71	28	0	1	0	0
	24 hrs. after	1.0	0.30	6.4	9300	60	36	2	2	0	0
	Sixth treatment										
	Before	0.9	0.30	4.3	8000	55	27	5	1	2	0
	Height of temp.	0.9	0.40	4.9	12200	71	28	0	0	1	0
	24 hrs. after	1.0	0.30	5.0	7400	65	33	1	0	1	0
	Eighth treatment										
	Before	0.9	0.30	5.1	9400	60	38	2	0	0	0
	Height of temp.	1.7	0.30	....	12000	65	32	1	2	0	0
	24 hrs. after	1.1	0.30	5.7	9200	47	48	3	2	0	0
12	First treatment										
	Before	2.1	0.80	4.3	8000	42	56	0	2	0	0
	24 hrs. after	3.5	0.30	4.6	6800	43	54	1	1	0	0
13	First treatment										
	Before	0.7	.....	5.7	8500	51	47	1	1	0	0
	Height of temp.	1.2	.....	5.6	15900	87	32	1	0	0	0
	24 hrs. after	1.0	.....	6.3	14000	63	36	1	0	0	0
	Fourth treatment										
	Before	0.7	.....	6.4	8800	54	42	0	3	1	0
	Height of temp.	0.8	.....	5.5	12900	83	16	0	1	0	0
	24 hrs. after	1.0	.....	4.9	8000	63	35	1	1	0	0
	Sixth treatment										
	Before	1.0	.....	5.3	7500	57	41	0	1	1	0
	Height of temp.	1.4	.....	....	....	....	....	....	....	....	....
	24 hrs. after	1.0	.....	....	11100	70	26	0	4	0	0
Eighth treatment											
Before	0.9	.....	5.6	8500	55	45	0	0	0	0	
Height of temp.	0.8	.....	5.4	11600	69	26	0	3	0	0	
24 hrs. after	0.9	.....	5.3	7000	60	40	0	0	0	0	
14	First treatment										
	Before	1.4	.....	5.3	6800	62	35	0	3	0	0
	24 hrs. after	1.2	.....	6.3	7100	57	40	1	2	0	0
15	Second treatment										
	Before	1.0	.....	....	....	....	....	....	....	....	....
	24 hrs. after	0.7	.....	....	....	....	....	....	....	....	....
16	First treatment										
	Before	0.9	.....	....	....	....	....	....	....	....	....
	24 hrs. after	0.9	.....	....	....	....	....	....	....	....	....
17**	First treatment										
	Before	1.5	0.25	....	9200	49	50	0	1	0	0
	Height of temp.	1.7	0.25	4.9	6300	74	26	0	0	0	0
	24 hrs. after	1.2	0.25	4.3	6900	48	47	1	3	1	0
	Second treatment										
	Before	1.1	0.30	....	5600	47	44	2	4	3	0
	Height of temp.	1.0	0.30	4.8	9900	60	37	0	1	1	1
	Sixth treatment										
	Before	0.9	0.30	4.7	8900	31	65	3	1	0	0
	Height of temp.	0.8	0.30	5.1	13000	53	45	2	0	0	0
	24 hrs. after	0.8	.....	....	8100	33	62	3	1	0	0
	Eighth treatment										
Before	1.1	0.30	4.3	7700	49	46	1	4	0	0	
Height of temp.	1.0	0.30	4.5	9700	60	37	1	2	0	0	
24 hrs. after	1.2	0.30	4.6	7400	59	42	3	1	0	0	

\* The percentage phagocytosis of the control serum and cells was unusually low. This may account for the apparently high values in Case 12.

\*\* Case 17 = General Paresis.

\*\*\* Poly. = Polymorphonuclear neutrophils.

L. = Lymphocytes.

E. = Eosinophiles.

Tr. = Transitionals.

M. = Mononuclears.

B. = Basophiles.

performing the opsonic test by dividing the percentage of phagocytosis occurring with patient's serum by that with normal human serum was used in the asthma cases.<sup>(13)</sup> In the arthritis and general paresis patients, in addition, the opsonins and phagocytic power of the patient's leucocytes were evaluated as described in a previous paper.<sup>(14)</sup>

*Agglutination.* Agglutination tests were done by the usual macroscopic dilution method.

**Results**

*Intractable Asthma* (Cases 1 to 9 inclusive). No consistent changes in complement titer or opsonic index were observed. What slight changes did occur cannot therefore be attributed to the effects of the temperature. (Table 1.)

*Infectious Arthritis* (Cases 10 to 16 inclusive) and *general paresis* (Case 17). In 13 out of 15 determinations made at the height of temperature there was an increase in the total number of leucocytes (Table 2). In only one instance did this leucocytosis last 24 hours. The increase was found to be in the number of polymorphonuclear neutrophils.

The percentage of lymphocytes decreased correspondingly. It has been suggested that the concentration of the blood might be the real cause. Since the erythrocyte count did not increase in proportion to the count of leucocytes, which was sometimes 100 per cent, and in view of the disproportionate change in the two types of white cells this is unlikely. In only 5 out of 35 tests was there even a slight increase in the opsonic index.

In examining the phagocytic property of a patient's leucocytes it is not compulsory that their number be constant because variations can be adjusted but the serum should be uniform throughout. This was possible in only three instances, 13 (8), 15 (2) and 16 (1), for these were the only ones tested with normal as well as with their own serum. Since, however, diathermy effected little, if any, change in the opsonins and, further, since the phagocytic power was ascertained in these cases (13, 14, 15, 16) both before and after treatment, the findings should be significant. The results are shown in Charts 1 and 2. It is readily seen that diathermy had no effect on the phagocytic property of the leucocytes. It is also apparent that when counts above

TABLE 3.—*Agglutination with Typhoid Vaccine Used in Treatment*

Treatment No.	Case 10						Case 11						Case 13						Case 14						
	10	20	40	80	160	320	10	20	40	80	160	320	10	20	40	80	160	320	10	20	40	80	160	320	
I	B	—	—	—	—	—	I	+	+	+	+	—	—	I	—	—	—	—	—	I	—	—	—	—	—
	Ht	—	—	—	—	—	+	+	+	+	+	—	—	—	—	—	—	—	—	—	—	—	—	—	
	A	—	—	—	—	—	+	+	+	+	+	—	—	—	—	—	—	—	—	—	—	—	—	—	
IV	B	—	—	—	—	—	VI	+	+	+	+	—	VI	—	—	—	—	—	—	—	—	—	—	—	
	Ht	—	—	—	—	—	+	+	+	+	+	—	—	—	—	—	—	—	—	—	—	—	—	—	
	A	—	—	—	—	—	+	+	+	+	+	—	—	—	—	—	—	—	—	—	—	—	—	—	
VIII	B	—	—	—	—	—	+	+	+	+	+	—	+	+	—	—	—	—	—	—	—	—	—	—	
	Ht	—	—	—	—	—	+	+	+	+	+	—	+	+	—	—	—	—	—	—	—	—	—	—	
	A	—	—	—	—	—	+	+	+	+	+	—	+	+	—	—	—	—	—	—	—	—	—	—	

B = Before treatment.  
Ht = Height of temperature.  
A = 24 hours after treatment.

TABLE 4.—*Agglutination with Bacillus Typhosus (Living Stock Strain)*

Treatment No.	Case 10						Case 11						Case 13						Case 14					
	10	20	40	80	160	320	10	20	40	80	160	320	10	20	40	80	160	320	10	20	40	80	160	320
I	B	—	—	—	—	—	I	—	—	—	—	—	I	—	—	—	—	—	I	—	—	—	—	—
	Ht	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IV	B	—	—	—	—	—	VI	—	—	—	—	—	VI	—	—	—	—	—	—	—	—	—	—	—
	Ht	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
VIII	B	—	—	—	—	—	VIII	—	—	—	—	—	VI	+	+	—	—	—	—	—	—	—	—	—
	Ht	—	—	—	—	—	—	—	—	—	—	—	+	+	+	—	—	—	—	—	—	—	—	—
	A	—	—	—	—	—	—	—	—	—	—	—	+	+	+	—	—	—	—	—	—	—	—	—

15,000 are used, the relation of the number of leucocytes to the percentage phagocytosis is no longer linear. (Chart 2.) This is in agreement with findings in experiments made with normal dog leucocytes.<sup>(15)</sup>

The figures for cases 13 (8), 15 (2) and 16 (1), in which we were able to study not only the phagocytic power of the patients' serum and cells but also the patients' cells with normal serum, indicate no noteworthy

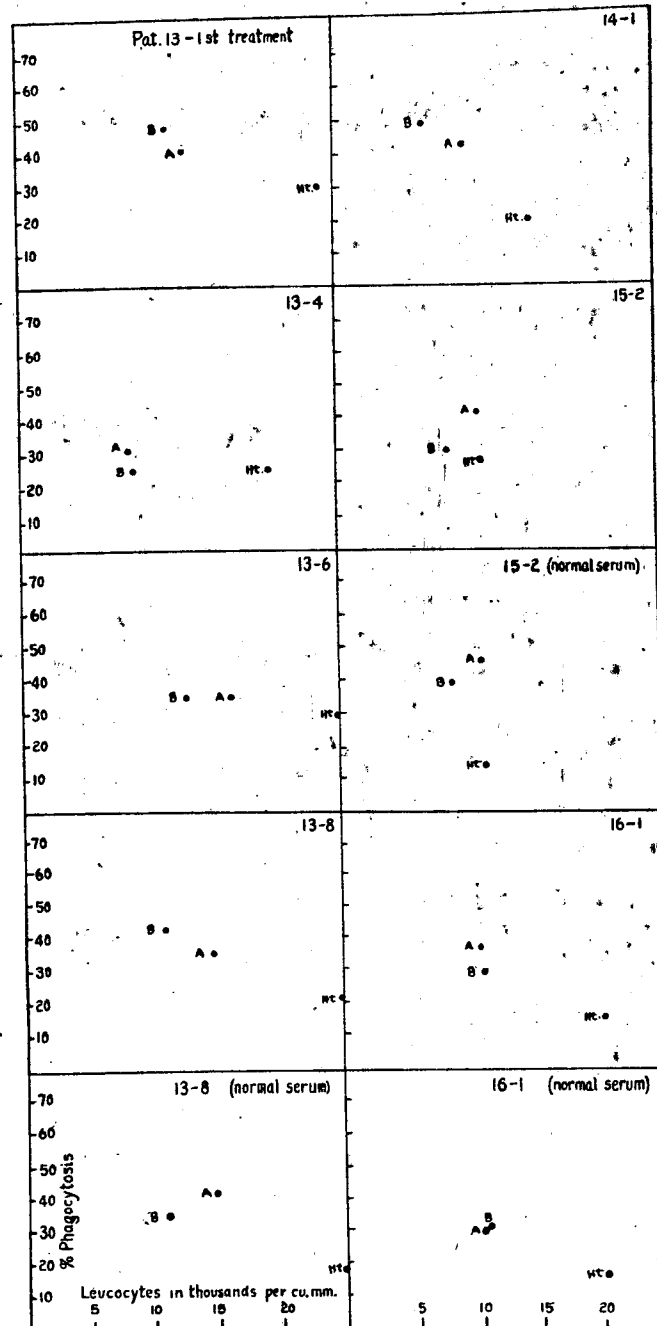


Chart 1. — Effect of Diathermy on Phagocytic Property of Patient's Blood. Case 13 (1st, 4th, 6th, 8th treatments); Case 14 (1st); Case 15 (2nd); Case 16 (1st) — Patient's serum and leucocytes. Case 13 (8th); Case 15 (2nd); Case 16 (1st) — Leucocytes also tested with normal serum.

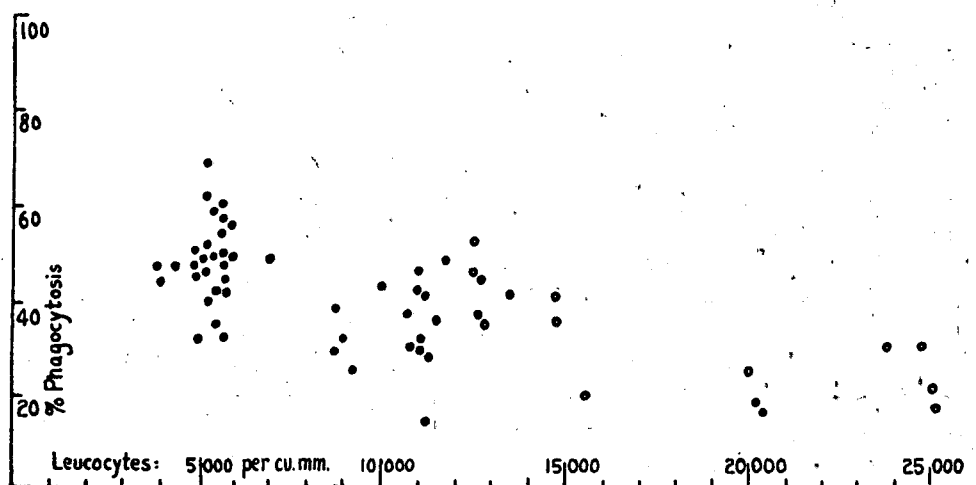


Chart 2.— Effect of Diathermy on Phagocytic Property of Patient's Blood which includes figures from Chart 1 and also figures showing percentage of phagocytosis by normal leucocytes and patient's serum.

differences whether normal or patient's serum was used. There is a suggestion of a change at the height of temperature in the phagocytic power of the leucocytes of patient 15 which is apparent with normal serum but not with the serum of the patient. The increase in the number of leucocytes in this case was slight. Cases 13 and 16 showed no marked differences when patient's or normal serum was used with the patient's leucocytes. A large series of cases treated in this manner might show significant variations.

Since the arthritis patients had received injections of typhoid vaccine for varying

lengths of time preceding their diathermy treatments, it was thought that there might be some changes in the agglutinins for *Bacillus typhosus* and perhaps for organisms in closely related groups. The sera of four patients (Cases 10, 11, 13, 14) were tested with the commercial vaccine used in their treatment. In addition the sera of all four were tried with a living laboratory strain of *Bacillus typhosus*, (Table 4) and cases 13 and 14 also with laboratory cultures of *Bacillus paratyphosus A* and *B* and *Bacillus coli* (Table 5).

Only one of the four (Case 11) showed any

TABLE 5.— Agglutination with *Bacillus Paratyphosus A*, *Bacillus Paratyphosus B* and *Bacillus Coli* (Living Stock Strains)

Case 13

Treatment No.		<i>B. paratyphosus A</i>						<i>B. paratyphosus B</i>						<i>B. coli</i>					
		10	20	40	80	160	320	10	20	40	80	160	320	10	20	40	80	160	320
I	B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Ht	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IV	B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Ht	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
VI	B	—	—	—	—	—	—	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	
	Ht	—	—	—	—	—	—	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	
VIII	B	++	+	—	—	—	—	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	
	Ht	+	—	—	—	—	—	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	
Case 14																			
I	B	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	Ht	—	—	—	—	—	—	+	+	+	—	—	—	—	—	—	—	—	

Controls negative in NaCl.

appreciable amount of agglutinins for the commercial vaccine (Table 3). There was a slight suggestion of an increase in agglutinins in patient 13 (Tables 3, 4 and 5). This was a gradual augmentation which occurred with succeeding treatments but at no time became at all marked. The greatest change took place in agglutinins for *Bacillus paratyphosus B*, with *Bacillus coli* ranking next.

#### Summary

The only significant immunologic change produced by diathermy in the blood of individuals suffering from intractable asthma, infectious arthritis, and general paresis was a temporary increase in the leucocyte count immediately after hyperpyrexia. This increase was in the polymorphonuclear neutrophils. In all but one out of fifteen determinations the count was normal in 24 hours. The erythrocyte count showed no notable changes. Alterations in complement content, opsonins and phagocytic property of leucocytes were found to be virtually within the limits of normal variation as established by the methods employed. There was an indication of a slight increase in agglutinins with succeeding treatments.

#### Conclusion

Whatever beneficial effects hyperpyrexia has in intractable asthma, general paresis and infectious arthritis are probably on a basis other than that of the phenomena studied.

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