7978 C

Prevention of Poliomyelitis in Monkeys by Means of Hyperpyrexia.*

HEINRICH F. WOLF. (Introduced by Maurice Brodie.)

The remarkable results of hyperpyrexia in various infectious diseases, particularly in gonorrheal infections, has turned the attention to its application in a great variety of disorders. The fact that the gonococcus can be destroyed *in vivo* as well as *in vitro* by temperatures compatible with life led me to the assumption that the same process may be effected in the treatment of virus diseases.

I concentrated my experiments on the treatment of poliomyelitis in monkeys and the object of this paper is to show that it is possible to prevent the development of poliomyelitis in monkeys completely or to affect the disease in such a way that the symptoms are only slight and disappear rapidly, if monkeys are treated immediately after inoculation, before symptoms have had time to appear.

The monkeys treated were inoculated by Dr. Maurice Brodie intracerebrally according to the technique and the system of infective doses worked out by him.

The hyperpyrexia was produced by a short wave apparatus operated by a spark gap and producing a wave of 16 meters. The electrodes consisted of 2 metal plates 6x8 inches placed side by side and covered with heavy cardboard. On this cardboard a cushion of sponge rubber was placed which assures an air space between the electrodes and the animal of about ¾ of an inch. The electrical field passes from one electrode to the other through the body of the monkey which is lying on the rubber cushion. After various trials the best method was found to be to tie the monkey to a board on its back and placing the board on the electrodes. The amount of field energy was about 2,000 M.A.

The rectal temperature of the monkey rises from normal, that is 101° to 103.4° to 107° and 108° within half an hour. Once the temperature of 108° to 108.6° is reached it is necessary to interrupt

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the treatment and resume it when the temperature has fallen to about 107°. The rise of temperature from 107° to 108° or more may be accomplished in 1 to 1½ minutes. It is, therefore, necessary to measure the temperature every minute or one and a half minutes when the current is on, so that the temperature may not rise above the tolerable limit, and every 5 minutes while the current is turned off, in order to forestall a great drop in temperature.

Monkey No. 650 received 10 M.C.P. on March 22nd; treated on the 24th, 25th and 27th of March. The animal received hyperpyrexia sustained above 107° for 4½ hours. The maximum temperature was 109° for a few minutes. The monkey did not develop any signs of disease.

Monkey No. 651, infected on the same day, March 22nd, with the same dose. Treated on March 24th, 26th and 27th. Hyperpyrexia with heat sustained above 107° for 3 hours. The maximum temperature was 109.5°. The animal did not develop any signs of the disease.

The control monkey, No. 647, infected with only 1 M.C.P. became prostrate on the 8th day.

Monkey No. 640, inoculated May 23rd with 10 M.C.P. Treated on May 25th, 27th, 28th, and 30th, hyperpyrexia above 107° sustained for about 3½ hours, total treatment given 7½ hours. The monkey showed a slight weakness of the right hand but recovered completely.

Control monkey No. 756 received between 1 and 2 M.C.P. and was prostrate after 5 days.

Monkey No. W-2, infected October 26th with 5 M.C.P. Treatment started October 27th and continued October 28th, 31st, November 3rd. Temperature sustained above 107° for more than 4 hours. The monkey showed no signs of disease.

Control monkey No. W-3, infected on the same day with the same dose became paralyzed and died October 31st.

Control monkey No. W-1, infected on the same day as W-2, and W-3, with the same dose. Treated first October 30th, temperature already 105.2°, second treatment October 31st, third treatment November 1st, received sustained heat of over 107° for about 4 hours. Showed slight facial palsy on November 1st, became paralyzed and died November 3rd.

Monkey No. 821, infected with 5 M.C.P. October 7th. Treated October 8th, 9th and 10th. On the third day of treatment the monkey showed severe diarrhea and general weakness and the treatment was discontinued. The monkey improved and no more treatments

TABLE I.
Treatment in Incubation Period with Controls.

Number	Date of Infect.	M.C.P.	Treatment No. of Days after Inoculation Incubation Stage	Preparalytic Stage	Duration of Treatment above Temp. of 107; Maximum Temp.	Outcome	Remarks
650	3/22	10	2 3 5		4½ hrs. in all; maxim. temp. 109	remained well	
651	3/22	10	2 4 5		3 hrs., maxim. temp. 109.5	,, ,,	
Control	3/22	1				died 7th day	
821	10/7	5	1 2 3*		3 hrs., maxim. 109	prostrate on 15th day	*Strong diarrhea, weak, temp. to 105
Control	10/7	3				prostrate 7th day	
W-2	10/26	5	1 3 6 9		6 hrs., maxim. temp. 108.6	remained well	
Control	10/26	5				prostrate 5th day	
,,	10/26	5		5 6 7	5 hrs., maxim. temp. 108	prostrate on 9th day	Showed slight signs of paralysis on 7th day
640	5/23	10	2 4 5 6		3½ hrs., total treatment 7½ hrs.	remained well	Right hand weak on 8th day, recovered
Control	5/23	1-2				died 8th day	

were given as no signs of poliomyelitis appeared. The monkey seemed perfectly well but suddenly became paralyzed on the 14th day. This greatly prolonged incubation period indicates that in view of the previous experience the animal could probably have been saved if the treatments had been continued.

The control monkey received 3 M.C.P. October 7th, was treated once on October 15th, body temperature 104.2°. Paralyzed on the next day.

To summarize the above experiments: Five animals were used in this series for experimental purposes and 5 for controls. Four monkeys were infected intracerebrally with 5 and 10 M.C.P., respectively, and treated 1 or 2 days after inoculation. None of these became paralyzed. One monkey showed slight weakness of one arm and recovered completely.

The control monkeys which were not treated at all or treated in the preparalytic stage *after the onset of fever* became prostrate. One which was treated energetically (No. W-3) showed a prolonged preparalytic stage.

One monkey which was infected with 10 M.C.P. and treated 1 and 2 days after inoculation in which the treatment had to be interrupted on account of diarrhea became prostrate on the 14th day. The control monkey which received only 3 M.C.P. and was given only one treatment on the 6th day (in the preparalytic stage) was prostrate on the 7th day. (Table I.)

From these experiments it seems to be definitely established that it is possible to abort the development of poliomyelitis in monkeys by hyperpyrexia if the treatments are given soon (1 or 2 days) after the inoculation and if they are continued over a sufficiently long time. The uniformity of results permits their publication in spite of the relatively small number of experiments.

In the following I should like to present a hypothesis for the action of hyperpyrexia. The assumption that its efficacy is due to a viruscidal action is obviously erroneous. If this were so we should expect results regardless of intensity of infection and the time elapsed between inoculation and treatment. It occurred to me that the unquestionable action might be explained in the following way:

The virus of poliomyelitis does not develop if the monkey is injected intravenously, obviously because it can not pass the blood-brain barrier and is destroyed in the blood. On the other hand if injected into the brain or nose it can exert its action on the nerve cells because the antibodies in the blood can not pass the barrier and destroy the virus. It may be possible that hyperpyrexia by dilation

of the capillaries makes the blood-brain barrier permeable to some extent for the antibodies and if these can attack the virus early in the incubation period they may neutralize the virus. Once the virus has had a chance to multiply and produce a reaction in the body in form of fever no results were obtained from hyperpyrexia if large infective doses were injected. Experiments not yet concluded on monkeys infected with small doses indicate that the size of initial dose is of great importance.

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Estrogenic Dihydroxy Compounds in the Urine of Pregnant Mares.

OSKAR WINTERSTEINER, ERWIN SCHWENK, AND BRADLEY WHITMAN. (Introduced by H. T. Clarke.)

From the Department of Biological Chemistry, College of Physicians and Surgeons, Columbia University, and the Research Laboratories of the Schering Corporation (Bloomfield, N. J.)

Schwenk and Hildebrandt[1] described the isolation from the urine of pregnant mares of a new compound of high estrogenic potency. This substance, designated by them δ-follicular hormone, melted at 209°, gave a characteristic purple color when coupled with p-nitrodiazobenzene and showed a gold yellow fluorescence in concentrated sulfuric acid solution. Analysis of the compound itself and of its mono-benzoate indicated the composition $C_{18}H_{22}O_2$. Treatment with ketone reagents failed to give characteristic derivatives.

Another batch of pregnant mare's urine has now been worked up in the laboratories of the Schering Corporation (Bloomfield, N. J.). The compound present in largest amount in the crude fraction containing the phenol-alcohols is the above δ-follicular hormone. Analysis of the present preparation gave figures agreeing better with $C_{18}H_{24}O_2$ than with $C_{18}H_{22}O_2$. The preparation of a di-p-nitrobenzoate (m.p. 260° uncorr.) leaves no doubt that both oxygen atoms are present in the form of hydroxyl groups.

A second substance isolated is apparently identical with the lower melting member (m.p. 174° uncorr.) of the pair of isomeric hydroxyphenols ("α-dihydrofollicular hormone") which Schwenk and Hildebrandt[2] obtained by reduction of theelin. It shows the same

[1] Schwenk, E., and Hildebrandt, F., *Naturwis.*, 1932, **20**, 658.

[2] Schwenk, E., and Hildebrandt, F., *Naturwis.*, 1933, **21**, 177.