THE EFFECTS OF INDUCED HYPERTHERMIA ON PATIENTS WITH MULTIPLE SCLEROSIS*

BY

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Several authors have reported that induced hyperthermia causes new neurological signs to develop in patients with multiple sclerosis. Collins (1938) observed that a patient with multiple sclerosis while receiving fever therapy developed a series of neurological signs that reversed when the fever therapy was terminated. Simons (1937) pointed out that 62% of patients with multiple sclerosis gave a history of becoming weak when exposed to heat. Guthrie (1951) found that neurological signs can develop in a patient with multiple sclerosis when only a leg or arm is immersed in hot water, and he pointed out the frequent diminution in visual acuity and the appearance of scotomata when patients are totally or partially immersed in hot water.

In an earlier study (Nelson, Jeffreys, and McDowell, 1958), we investigated the effects of induced hyperthermia by hot baths not only on patients with multiple sclerosis but on patients with a variety of other diseases of the nervous system. It was found that each of the 12 patients with multiple sclerosis developed neurological changes and that these were usually multiple (an average of 2.8 per patient). It was also found, however, that 55% of patients with diseases other than multiple sclerosis developed neurological changes. These were usually single signs and tended to occur at higher elevations of body temperature than in patients with multiple sclerosis. Patients with multiple sclerosis frequently developed alterations in extraocular movements, including the appearance of nystagmus, signs of dysfunction of the medial longitudinal fasciculus, and paralysis of extraocular muscles. Visual acuity also frequently decreased. It was found that three patients with multiple sclerosis developed signs before any elevation of body temperature was recorded. Because of the possibility that this may

have been due to the manner in which the test was performed (taking the oral temperature every five minutes), the present study was undertaken to study the occurrence of neurological changes in patients with multiple sclerosis with particular attention to the temperature of onset.

Methods and Materials

Fourteen patients with a clinical diagnosis of multiple sclerosis were studied. Two of these were confined to bed and had far advanced disease; 12 were ambulant and had moderately advanced disease. There were eight women and six men in the study. Their average age was 42 years with a range from 29 to 57 years. The duration of the disease varied from two and a half years to 28 years. Eight patients (57%) gave a history of intolerance to heat, usually profound weakness in a hot bath.

Their body temperatures were raised in two different ways. Five patients were heated with infra-red lamps which arched over the bed two feet from the skin and radiated the patient from the nipple line down. The patient was covered with a blanket in order to raise humidity and to reduce the cooling effects of sweat evaporation. Skin and rectal temperatures were recorded using skin and rectal thermocouples. In this manner the skin temperature was raised to between 114 and 117°F. and the rectal temperatures were raised from 1.5 to 4.7°F. in 30 to 72 minutes.

Nine patients were heated by immersing them up to the nipple line in a hot bath with the water temperature at 105°F. and then elevating the temperature of the bath to 106 to 110°F. over a 10 to 15-minute period. Body temperature was recorded utilizing a rectal thermocouple and rectal temperatures were elevated from 1 to 4°F. in 23 to 40 minutes. The thermocouple was introduced 6 in. or more into the rectum and the buttocks were taped together to prevent any water from entering the anus.

These two techniques were utilized as a means of gradually elevating the body temperatures so that careful note could be made of the body temperature at which new signs occurred. Blood pressures, visual acuity, pupillary size, dysarthria, nystagmus, range of extraocular movements, and evidence of weakness of the extremities were

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recorded. A previous study (Nelson *et al.*, 1958) indicated that the most frequent neurological changes were diminished visual acuity and changes in extraocular movements, and led us to concentrate on these observations. Changes in reflexes, strength, coordination, etc., may have occurred during this study but due to their inconsistent change in the first study and difficulty in evaluating and recording them, they were not included. After discontinuing heating, the patients were examined at intervals until control levels of body temperature and neurological signs were reached. Visual acuity was measured with a Snellen chart at 15 feet in the patients who were heated with the lamps and the other patients who were heated in the bath had visual acuity measured utilizing a Lebensohn near-vision chart.

Results

Table I indicates the type of neurological signs observed and the frequency with which they appeared in these 14 patients when their body temperatures were raised from 1°F. to 4.7°F. It can be seen that

TABLE I
TYPE OF NEUROLOGICAL CHANGES

Type of Sign	No. of Signs
Diminished visual acuity	9
Horizontal nystagmus*	7
Vertical nystagmus*	6
Diplopia	4
Medial longitudinal fasciculus syndrome	4
Dysarthria	3
Paraparesis	3
Upward gaze palsy	1
Rectus muscle palsy	1

*Not present at beginning of test.

diminished visual acuity and changes in extraocular movements accounted for the majority of the changes. One patient developed no measurable signs, three developed only one sign, but the others developed an average of three new signs. The patient who developed no signs had evidence of a transverse myelopathy and never had had evidence of cranial nerve dysfunction. The three patients who developed only one sign also had predominantly evidence of spinal cord involvement. One developed paraparesis, one developed horizontal nystagmus (there was an earlier history of vertigo during exacerbations), and the other patient developed loss of visual acuity. This last patient had no earlier history of loss of visual acuity and had never shown it on prior examination. This is the only patient in this or the earlier study who developed a sign of dysfunction of the nervous system without some earlier evidence or history of similar dysfunction.

There were eight patients who were in remission, the last change in neurological status dating from six months to six years before the heat study. Six patients were in an active stage of the illness at the

TABLE II
RELATION OF BODY TEMPERATURE TO NUMBER AND OCCURRENCE OF SIGNS IN PATIENTS WITH ACTIVE AND INACTIVE MULTIPLE SCLEROSIS

Patient	Body Temperature Elevation at Appearance of First Sign	Total No. of Signs
<i>Patients in Remission</i>		
1	0.3	2
2	1.3	3
3	—	0
4	2.2	3
5	2.7	1
6	2.0	2
7	1.9	1
8	0.9	1
<i>Patients in Exacerbation</i>		
1	1.6	3
2	1.6	3
3	1.3	4
4	0.3	5
5	0.5	5
6	0.9	4

time of the study. Table II shows a comparison between these two groups and the temperature elevation at which the first sign occurred and the number of signs which developed. These figures suggest that the patients who were in remission showed fewer signs and that the elevation of body temperature at the appearance of the first sign was higher than for those patients with evidence of activity of the disease at the time of the study.

All patients who developed neurological changes showed an elevation of body temperature before the appearance of the first of these signs. It varied from 0.3°F. to 2.7°F. The patients who received infra-red heat showed the first sign at a mean exposure time of 42 minutes compared with a mean immersion time of 20 minutes in the other group. Neurological signs appeared at this range of temperature elevation regardless of whether the patient was heated very slowly (as with infra-red lamps) or rapidly (as in hot water).

To further investigate whether these neurological changes depend upon an elevation of body temperature or were perhaps due to the stress of the test situation, the following studies were done.

One patient (K.B.) had developed the first sign (nystagmus on lateral gaze) after 24 minutes of radiant heat when her body temperature had been raised 1.6°F. She was placed in a hot bath for two hours and 15 minutes. Her body temperature was not allowed to rise more than 1.6°F. during the period and no neurological changes occurred. When her body temperature was allowed to rise 1.7°F. at the end of this study she developed nystagmus, which disappeared when her body temperature fell again to 1.6°F. Similar results occurred in another patient who had shown his first sign in the bath after 23 minutes when his body temperature was raised by 1.3°F. This patient was studied at

a later date in the warm bath, at which time his body temperature was raised 0.4°F. to 0.9°F. for one hour and 50 minutes. During this time no changes in the neurological examination occurred. A third patient was very sensitive to heat and had shown a first neurological change at 0.5°F. body temperature elevation after seven minutes of immersion in the hot bath. This was checked a second time with only the feet and legs immersed in hot water. On this examination the first sign occurred at 0.4°F. after eight minutes of immersion. In this patient, who was very sensitive to heat, changes did occur with partial immersion but not until there had been the same body temperature elevation as during the first test.

Comparison of blood pressure changes between the patients who received radiant heat and those who received heat by hot water revealed that those in the group heated by infra-red lamps showed blood pressures which remained the same or showed slight elevation, and in the other group, though the diastolic blood pressures fell significantly, there was no significant difference in the numbers of signs which developed.

Neurological signs which appeared on exposure to heat tended to revert to control levels while the body temperature was above that at which the first sign occurred. Table III compares the body temperature elevation at which the first sign occurred

TABLE III
RELATIONSHIP OF APPEARANCE AND DISAPPEARANCE
OF NEUROLOGICAL SIGNS TO ELEVATION OF BODY
TEMPERATURE

Patient	Body Temperature at First Sign (°F.)	Body Temperature at End of Test (°F.)	Body Temperature at First Sign of Disappearance (°F.)	Body Temperature at Last Sign of Disappearance (°F.)
<i>Immersion in Hot Water</i>				
1	1.3	2.2	2.2	2.0
2	0.3	1.0	1.0*	1.0
3	2.2	3.8	3.8	3.3
4	2.7	2.8	2.8*	2.8
5	2.0	2.5	1.2	1.0
6	0.5	0.7	0.5	0.5
7	0.9	1.3	2.4*	2.4
8	0.9	1.7	1.7	1.4
<i>Radiant Heat</i>				
9	0.3	0.5	-0.3	-0.3
10	1.9	4.2	4.3*	4.3
11	1.6	2.3	1.8*	1.8
12	1.6	2.6	2.2	1.7

*All signs disappeared at the same temperature.

with the temperature at which the first sign disappeared and that at which the last sign disappeared. Twelve patients are reported, for one developed no change in signs and data on one are lacking. In nine of these 12 patients the neurological changes disappeared when body temperature was above that

at which the first sign appeared. Two patients had neurological signs reversed while the body temperature was still climbing.

Discussion

Eight of the patients in this series gave a history of weakness on exposure to heat. Seven gave a history of generalized weakness in hot baths (one of these also had dysarthria) and one gave a history of weakness of the legs only. Our patients had often found it necessary to give up hot baths due to severe weakness and the inconvenience of lying helpless in the water until someone arrived to give them assistance in leaving the tub.

It appears that most patients with multiple sclerosis will develop one or more additional neurological signs when their body temperatures are raised 0.5°F. to 2.5°F. A particular temperature elevation seems necessary before signs appear, and changes apparently do not occur as a result of the stress of the test or drop in systemic blood pressure. The additional signs which appear have with one exception occurred during an active phase of the illness in the past. The signs which appear during induced hyperthermia disappear when the patient is cooled, but often when the body temperature is at a higher level than that at which the first signs appeared. This suggests that there is some type of adaptation during heating.

The aetiology of these neurological changes is obscure. It may be the heat itself which causes dysfunction in parts of the nervous system which have suffered prior damage by demyelinating plaques. Elevation of the body temperature to a certain level may also release a humoral substance which acts on nervous tissue.

Though the appearance of neurological signs upon elevation of body temperature is by no means specific for multiple sclerosis, the appearance of multiple signs when the body temperature is elevated between 0.5°F. and 2.5°F. speaks in favour of this diagnosis. These studies also indicate that signs of neurological dysfunction are more likely to occur after elevation of the body temperature when the disease process is active.

Summary and Conclusions

Eight of 14 patients with multiple sclerosis gave a history of weakness when exposed to heat or hot baths.

Thirteen of 14 patients developed neurological signs when the body temperatures were elevated $1.3 \pm 0.7^\circ\text{F}$.

Ten patients developed multiple signs. Three patients developed single signs and these patients

mostly showed evidence of spinal cord damage on neurological examination.

The occurrence of neurological changes seemed to be related only to the body temperature elevation and not to length of exposure or to depression of blood pressure.

Changes most frequently found were ocular motility changes and diminution in visual acuity.

Nine patients showed a reversion to the control observations when the body temperature was

above that at which the first neurological sign appeared.

The appearance of new neurological signs after raising the body temperature is more frequent when the disease is active.

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