

THE EFFECT OF HYPOTHERMIA ON METASTASIS OF BROWN-PEARCE TUMORS

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Cooling of the body as a whole was first used clinically as a method of influencing the growth of malignant tumors by Fay, Henny and Smith in 1938-1944 [17, 18, 20]. These workers made observations on 175 patients suffering from advanced forms of malignant disease, and came to the conclusion that general cooling of the body to a temperature of 27-29°C causes retardation of growth of the tumor and delays the development of metastases. Other workers came to similar conclusions: McCravey [19], Vaughan [22], Talbot [21] and others.

Nevertheless this method has not been widely used in oncological practice, since cooling has itself been found to be dangerous to the patient's life. The danger of cooling to higher animals is that when the temperature falls, a defensive reaction develops in the body which aims to maintain the body temperature at a constant

Serial No	Rabbits No.	Spermatic cord		Mesentery	Serosa				Parietal peritoneum	Diaphragm	Omentum	Kidney		Liver	Spleen	Adrenals		Mediastinum	Lungs	
		left	right		Large intestine	Small intestine	Large intestine	Small intestine				right	left			right	left		right	left
Experimental animals																				
1	265	●●●	●	●	●	●	●	●	●	●	●	●	●						●●	●●
2	255	●●●	●●●	●	●	●	●	●	●	●●●	●●●								●●	●●
3	270	●●●		●	●	●	●	●	●	●									●●	●●
4	257	●●		●	●	●	●	●			●			●●●				●	●●	●●
5	267	●●●	●	●	●	●	●	●	●		●									
6	269	●●●		●●	●	●	●	●	●		●									
7	254	●		●●			●				●									
Control animals																				
1	258	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●	●	●	●	●●●	●●●
2	272	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●				●●●	●●●
3	266	●●●	●●	●●	●●	●●	●●	●●	●●	●●●	●●	●●							●●●	●●●
4	273	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●							
5	256	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●							
6	262	●●●	●●●						●●			●	●							
7	260	●																		
8	264																			

Fig. 1. Metastasis of a Brown-Pearce tumor in rabbits after six applications of hypothermia (1st series of experiments).

Serial No.	Rabbit No.	Sper-matic cords		Mesen-tery		Serosa		Parietal per-itoneum	Diaphragm	Omentum	Kid-neys		Liver	Spleen	Ad-renals		Mediastinum	Lungs	
		left	right	Large Intestine	small Intestine	Large Intestine	Small Intestine				right	left			right	left		right	left
Experimental animals																			
1	284	●●●	●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	○	○							
2	275	●●●		●●●	●●●			●●●	●●●	●●●	●●●	●●●	●●●		○	○		○●	○●
3	276	●●●	●●					●●●	●●●	●●●			●			○		○	○
4	281	●●		●	●			●	●●●	●●	○●	○●							
5	292	●●		●●●	●●●					●●●	○	○	●●						
6	283	●●	●	●	●			○●●	●●	●									
7	277	●●	○	●	○			●		●●									
8	307	●●	●●	●●	●			●●											
9	295	●●●	●					●●											
10	278	●																	
11	288	●																	
Control animals																			
1	296	●●●	●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●	●●	●					○●●	○●●
2	289	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●●	●●					○●●	○●●
3	282	●●●	●●	●●	●	●		●●●	●	●●●	●●●	●●●	●●					○●	○●
4	302	●●●	●●	●●	●●			●●●	●●●	●●●	●●●	●●●	●		○			○●	○●
5	279	●●●	●●●	●●	●●	●		●	●●●	●●●	●●●	●●	●						
6	293	●●●	●●					●●●		●●	○●●	○●●	○●●			○		○●	○●
7	285	○●	●	●	○●	○		●●●	○●	●●									
8	298	●●	●	●	○	○		○●	●●	●●									
9	303	●●●	●●					●	●●●	●●									
10	286	●	○					●●	○●										
11	305									●	○	○							
12	291														●				
13	290																		
14	294																		

Fig. 2. Metastasis of a Brown-Pearce Tumor in rabbits after six applications of hypothermia (2nd series of experiments).

level which is required for the normal vital activity of the more highly organized animals. The development of this defensive reaction is associated with marked stimulation of metabolism, excitation of the sympathetic nervous system, increased secretion of adrenalin and an increase in the oxygen demand of the body. All this leads eventually to exhaustion of the body's resources of energy and to the development of profound limiting inhibition in the central nervous system [1, 4, 7 and others].

In recent years the method of hypothermia has been applied on a wide scale in a number of clinics, mainly surgical during traumatizing operations. In order to produce a state of hypothermia the majority of workers use a combination of physical cooling, anesthesia and drugs which block the autonomic nervous system. It has been found that such a combination reduces the danger of the cooling itself and is therefore the best method of producing hypothermia [3, 9 and others].

A malignant tumor, as a part of the body, is known to be dependent on the state of the body as a whole and on the state of its metabolic processes. Any change in this state affects the growth and development of the tumor [2, 8, 10, 12, 13 and others]. It may therefore be postulated that a change in the processes of metabolism in the body due to the action of low temperatures will also modify the development of the tumor.

The experimental research on this problem [5, 6, 14-16 and others] is unfortunately very scanty and very conflicting.

Comparative Incidence of Metastases in Various Organs of Cooled and Control Animals (1st and 2nd series of experiments)

Organs	Incidents of involvement of individual organs (in %)	
	in the experiment	in the control
Spermatic cords:		
left	100	77.2
right	50.0	72.7
Mesentery		
large intestine	77.7	54.5
small intestine	72.2	54.5
Serous membrane:		
large intestine	44.4	45.4
small intestine	16.6	27.2
Parietal peritoneum	72.2	68.1
Diaphragm	33.3	58.0
Omentum	77.7	68.1
Kidneys:		
right	33.3	40.9
left	33.3	40.9
Liver	22.2	31.9
Spleen	—	22.2
Adrenals:		
right	5.5	4.5
left	16.6	18.1
Lungs:		
right	26.0	36.0
left	26.0	36.0

In view of the foregoing we carried out investigations of the process of metastasis formation in association with the metabolic changes of hypothermia.

EXPERIMENTAL METHOD

Hypothermia was produced by a combination of physical cooling, anesthesia and injection of neuroplegic drugs. Experiments were carried out on 40 rabbits (grey chinchilla breed, weight 2100-2850 g; 18 experimental and 22 control animals). The experiments were performed in 2 series. Under aseptic conditions a Brown-Pearce tumor was implanted in the left testicle of all the rabbits, in the form of 0.6 ml of a 20% suspension of the tumor in physiological saline. For the inoculation we used metastatic nodes from the peritoneal cavity of rabbits killed on the 21st day after inoculation of this strain of tumor.

Hypothermia was produced as follows. A 25% solution of urethane was injected into the vein of the left ear (dose 0.8 g per 1 kg body weight). Two minutes after sleep developed an intramuscular injection of 0.1% chlorpromazine solution was given (1 mg per 1 kg body weight), with the addition of 0.1 ml of a 0.1% solution of atropine. The animal was then bound to a frame and ice-bags applied. After 20 minutes a further injection of half the previous dose of chlorpromazine was given. The temperature was measured by a mercury thermometer in the rectum every 30 minutes. As a rule the animal remained in a state of sleep throughout the experiment. From 1½

to 4 hours after the beginning of cooling the body temperature fell to 28-27°C.

Each rabbit of the experimental group was cooled 6 times, on the 3rd, 6th, 9th, 12th, 15th and 18th day after inoculation of the tumor. All the animals of the control and experimental groups were killed 21 days after inoculation. Throughout the experiment the experimental and control animals were kept on identical diets.

In our study of the process of metastasis formation we compared the incidence and degree of metastasis formation in individual organs in the cooled and control animals. We assessed the degree of metastasis formation by the number and size of the metastases in the organs. The size of the metastases is shown on the records as follows: metastatic nodes measuring up to 0.2 cm in diameter are indicated by a ring, those measuring from 0.2 to 0.5 cm in diameter — by a black circle, and those over 0.5 cm in diameter — by an oval. The number of metastases is indicated by the number of rings: up to 10 metastases in the organ — by one ring (solitary metastases) from 10 to 30 metastases — 2 rings (moderate number of metastases) and over 30 metastases in the organ — by 3 rings of the appropriate pattern (multiple metastases).

EXPERIMENTAL RESULTS

The experimental findings show that metastasis formation differed considerably in the experimental and control animals: in the experimental group of rabbits the degree of metastasis formation was less than in the controls. In the 1st series of experimental animals, for instance, large metastases were present in the various organs 13 times, and in the control group — 24 times. Metastases of moderate size were present in various organs of the experimental group of animals 19 times, and in the control group 29 times. Small metastases were observed in the organs of 23 experimental animals and of 9 controls.

The same relationship was noted when the number of metastases in the organs of the animals of the experimental and control groups was compared. In the experimental group, for instance, multiple metastases were present in the various organs of 8 animals, and in the control group, of 40 animals. A moderate number of metastases were observed in the organs of 9 experimental animals and 13 controls. Solitary metastases were seen in the organs of 38 experimental and 9 control animals (Fig. 1).

Precisely the same results were obtained in the 2nd series of experiments, in which the same method was used (Fig. 2).

The experimental results thus showed that in the rabbits undergoing hypothermia, small and solitary metastases were preponderant, whereas in the control animals the majority of the metastases were multiple and large in size.

The comparative incidence of metastases in the various organs of the cooled and control animals is shown in the Table (1st and 2nd series of experiments).

As seen from the table, no clear difference in the incident of involvement of individual organs of the experimental and control groups could be observed. However it may be pointed out that in the control animals metastases were more often observed in organs affected by hematogenous spread (liver, kidneys, lungs and so on), whereas in the experimental animals these organs were less commonly involved.

The results described are in agreement with earlier observations on the effect of one, two and three applications of hypothermia on the formation of metastases and the length of survival of experimental animals. In these investigations there was a fall in the intensity of metastasis formation and an increase in the average length of survival in the animals subjected to the hypothermia. It may be assumed from these findings that hypothermia delays the growth of metastases.

SUMMARY

The effect of hypothermia induction (6 times) on the metastasis of Brown-Pearce tumor was studied. Hypothermia was attained by employment of physical cooling combined with the administration of aminazine, urethane and atropine. The degree of metastasis was compared in experimental and control rabbits in 21 days after the transplantation. It appeared that the induction of hypothermia decreases the degree of metastasis.

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