Coagulation During Hypothermia in Man.* (23689)

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The possibility of disturbances in coagulation during hypothermia is well recognized. It has been demonstrated that total body cooling in dogs is associated with marked disturbances in *in vitro* clotting tests(1,2,3) and frequently with frank hemorrhage(2). On the other hand, hemorrhage has not been a common problem in man during or after surgery performed at hypothermic temperatures. In the present report coagulation studies are presented on 10 patients before and after slow cooling and during surgery at lowered body temperature. Clotting time, platelet count, thromboplastin generation, prothrombin consumption, prothrombin time (Quick), and prothrombin, accelerator globulin, proconvertin and fibrinogen concentrations were determined. Although the clotting times of various coagulation tests were prolonged with blood or plasma incubated at the lowered body temperatures, the concentration of coagulation factors remained essentially normal during uncomplicated hypothermia (Temperature 29.1°C-31.0°C).

Material and methods. Ten patients were studied, 5 women and 5 men. Their ages ranged between 18 and 70 years. The diagnoses were cerebral vascular aneurysm (4 patients), meningioma (3 patients), cerebellar hemangioblastoma (1 patient), and thoracic aortic aneurysm (2 patients). Anesthesia was induced with intravenous thiopental sodium and nitrous oxide. Intubation was accomplished with the assistance of intravenous succinyl-choline 40-60 mg. The patients were cooled slowly (3-4 hours) by means of surface ice packs and rendered apneic with intravenous d-tubocurarine to prevent shivering. Hyperventilation was achieved by controlled respiration with the Jefferson Ventilator. Intravenous fluids during the period of cooling were limited to a slow infusion of 200-400 cc normal saline or 5% dextrose in water. An intravenous infusion of Arfonad (trimethaphan) 0.1% was used in 5 patients to control excessive blood pressure elevation. *Blood samples* were drawn: (1) after induction of anesthesia but before cooling; (2) after 3-4 hours of cooling, shortly before or after the beginning of surgery, and before the transfusion of blood; esophageal temperature at this time varied between 29.1°C-31.0°C; (3) near the end of surgery, 3-5 hours after second sample, temperature 27.3°-30.8°; 500-4000 cc of fresh blood collected by passage across the Fenwal cation exchange resin was administered between samples No. 2 and 3. Blood was obtained using untreated syringes and needles. When plasma was required, 9 volumes of blood were mixed with 1 volume of anticoagulant.† The cells were sedimented at 2000 rpm‡ for 20 min. in ordinary glass tubes. Thromboplastin generation was assayed by the method of Biggs and Douglas(4), as modified by Alexander and Goldstein. Asolectin was used as a substitute for platelets. Prothrombin consumption was determined by the method of Alexander(5). Platelets were counted by the direct Rees and Ecker method (6). Prothrombic activity was studied by the Quick one-stage method using Simplastin§ as a source of calcium and tissue thromboplastin(7). Accelerator globulin was determined by the method of Alexander(8). Proconvertin and prothrombin concentrations were determined by a modification of Owren's method(5). Fibrinogen was determined quantitatively by the method of Cullen and Van

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† 0.1M sodium oxalate was used for thromboplastin generation test, and 3.8% sodium citrate for prothrombin, proconvertin and Ac-globulin tests.

‡ International Centrifuge, Size 1, Type SX, International Equipment Co., Boston.

§ Available from Warner-Chilcott Lab.

Slyke(9). Fibrinolytic activity was estimated by inspection of the whole blood clot after 1, 2, 4, 12 and 24 hours of incubation at 37.5°C. Coagulation tests were carried out in a water bath at 37.5°C and at the temperature of the patient. Only data obtained at 37.5°C are included in the table.

Results are presented in Table I. In the absence of surgery or blood transfusion, hypothermia (29.1°-31.0°) was not associated with significant disturbances in any of the specific clotting factors measured. During hypothermia, surgery and transfusions, a variety of moderate disturbances in factors of the 1st and 2nd stages of coagulation was observed. With the exception of depression of prothrombin consumption, these disturbances were similar to those observed by us during surgery and transfusions in patients at normal body temperature. The depression of prothrombin consumption, marked in 3 and moderate in 3 other patients, could not be explained by the degree of thrombocytopenia, or by the alteration in thromboplastin generation encountered in 2 patients. However, a qualitative change in platelets was not ruled out, and plasma factors involved in thromboplastin formation were not measured individually.

Prolongation of the clotting times for all coagulation tests except whole blood clotting times was consistently observed when performed at the hypothermic temperatures rather than at 37.5°C.

Postoperative clotting studies were performed in 2 patients: 3 hours, 1, 3, and 7 days following surgery in one; 1, 2, and 7 days in the other. Moderate depression of platelets and Ac-globulin, present at the end of surgery in one of the 2, persisted for the first and second postoperative days, but returned to normal or somewhat above normal levels at the end of one week. Both patients demonstrated moderate increases in most clotting factors by the 7th day, and one showed a moderate thrombocytosis (264,000 preop. to 416,000 on 7th day).

Discussion. The normal concentration of coagulation factors during uncomplicated hypothermia observed by us in man clearly differs from results of similar studies in the experimental animal. Moderate to marked depression in platelets(1,2) and in accelerator globulin, proconvertin, prothrombin, and fibrinogen(3) have been described in the hypothermic dog. Whether the difference in findings is due to the lower temperature induced in most of the animal experiments (20-25° compared to 27-31°C) or to a species difference is not known. That the degree of hypothermia may be a significant factor is suggested by animal experiments in which the degree of thrombocytopenia was directly related to the degree of hypothermia(1). Marked thrombocytopenia usually occurred only below 25°C and was then associated with marked elevation in clotting times and depression of prothrombin consumption. However, in dogs, even at the temperatures used for hypothermia in man, more constant depression in platelets is observed and hemorrhage has been encountered; thus it seems likely that a species difference may exist, since hemorrhage is an unusual complication of hypothermia in human beings. There has been no evidence of unusual bleeding during surgery, and no postoperative hemorrhage, in any of 28 patients who have been subjected to hypothermia in this hospital. Occasional postoperative hemorrhage has been reported by Swan(10), who concluded that the "hypotension accompanying hypothermia" may have prevented bleeding from cut vessels which later bled when pressure returned to normal. In our experience, based on direct pressure tracings from an inlying arterial needle, the blood pressure often rises, but rarely falls during hypothermia. It is perhaps more likely that the occasional occurrence of posthypothermia bleeding is secondary to reflex vasodilation of subcutaneous vessels during the rewarming period.

It should be mentioned that an intravenous infusion of Arfonad (trimethaphan) was used in 5 of the 10 patients to control marked elevations in systolic blood pressure. Arfonad has been reported by Helmsworth(11) to afford partial protection against the thrombocytopenia of hypothermia in dogs. No correlation could be found in the present studies between Arfonad administration and the degree of thrombocytopenia (Table I).

Although we have been unable to find evi-

TABLE I. Coagulation Factors during Hypothermia.

Case No.	Temp. at sampling (°C)			Clotting time (min.)			Platelets (1000/mm³)			Prothrombin consumption (%)			Thromboplastin generation§			Quick prothrombin activity (%)			Owren prothrombin conc. (%)			Accelerator globulin (%)			Proconvertin (%)			Fibrinogen (g %)‡		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
1‖	37.5	29.5	28.8	13	13	11	252	452	212*	86	99	99				78	98	70	78	78	70				100	100	74	.52	.52	.40
2¶	36	31.5	27	15	9	14	328	336	132	92	81	56				100	88	85	90	83	95	100	81	60	100	82	92	.46	.41	
3¶	37.5	29.8	28.4	12	12	12	226	180*	82	96	73	54	N	N	N				100	100	100	100	100	100	100	100	86	.43	.41	.28
4‖	37.5	31	28	11	6	10	282	316	188	94	88	56	N	N	A	97	100	88	100	100	80	100	100	84	100	100	80	.43	.41	
5‖	36	29.1	30.6	10	12	11	124	102	120†	90	91	68							100	100	100	30	28	13	62	33	36	.35		.20
6‖	36		30.2	11		13	178		119	83		70	N		N	68		58	98		88	96		84	76		72			
7‖	36	31	27.3	12	15	19	173	127*	119*	95	91	74	N	N		76	65	29	100	100	100	100	94	74	100	86	80	.29	.27	.32
8‖	37.5		28.2	15		12	269		123†				N		A	90		70	100		96	92		64	98		79	.47		.33
9‖	37	30.9	30.8	12	9	14	264	324	258	98	94	94	N	N	N	100	100	96	100	86	92	100	100	100	86	100	100	.53	.46	.42
10‖	38	30.5	28.7	14	11	11	220	322	182	99	93	91	N	N	N	100	51	83	100	94	90	100	98	75	100	98	100	.86	.72	.50

A = before cooling; B = hypothermia, no transfusion; C = hypothermia, surgery, and transfusion.
* Patient receiving Arfonad (trimethaphan) 0.1% infusion at time of sample.
† Patient received Arfonad earlier, but not at time of sample.
‡ No fibrinolysis observed in any patient.
§ N = Normal; A = Abnormal.
‖ Craniotomy.
¶ Aortic graft.

dence that the concentrations of clotting factors fall during hypothermia in man, it is clear that the "activity" of all factors is depressed at these lower temperatures. It is, perhaps, surprising that frank bleeding does not occur as a result; on the other hand, it may be fortunate that a temporary slowing of coagulation does occur to lessen the possible danger of thrombosis occasioned by the slowing of circulation which accompanies hypothermia (12).

Marked shortening of whole blood clotting times in patients 2 and 4 (Table I) suggested the possibility of hypercoagulability or perhaps intravascular coagulation, but there were no other coagulation changes to support such a hypothesis. Similar shortening of whole blood clotting time has been observed by us in approximately the same frequency in normothermic patients undergoing anesthesia and surgery.

The possibility of thrombosis is important to consider and "intravascular clotting" has been implicated by Ellis as the explanation for the fall in all coagulation factors he observed in dogs(3). However, recently it has been demonstrated that the drop in platelets in dogs is due to a sequestration of platelets and not to their consumption or destruction (13). In our series of patients, 4 suffered postoperative thrombosis of cerebral vessels. Operative trauma during craniotomy was thought to be the causative factor, but a slowed cerebral flow may have contributed. The rôle of increased concentrations of clotting factors, observed in 2 patients postoperatively, must also be considered. However, there is no evidence at present that the "hypercoagulability" after hypothermia is different from that following any operative procedure.

Summary. Clotting times, platelets, thromboplastin generation, prothrombin consumption, prothrombin time, and concentrations of prothrombin, accelerator globulin, proconvertin, and fibrinogen were measured in 10 patients after the slow induction of hypothermia and later during surgery and transfusion. In contrast to previous studies in the dog, uncomplicated hypothermia in man was not as-

sociated with a fall in concentration of clotting factors. Moderate disturbances in coagulation with surgery and transfusion during hypothermia were in most regards similar to those observed during surgery and transfusion at normal body temperature. The one significant difference was a decrease in prothrombin consumption.

1. Villalobos, T. J., Adelson, E., Barila, T. G., PROC. SOC. EXP. BIOL. AND MED., 1955, v89, 192.

2. Helmsworth, J. A., Stiles, W. J., Elstun, W., *Surgery,* 1955, v38, 843.

3. Ellis, P. R., Kleinsasser, L. J., Speer, R. J., *ibid.,* 1957, v41, 198.

4. Biggs, R., Douglas, A. S., *J. Clin. Path.,* 1953, v6, 23.

5. National Research Council, *Coagulation of Blood: Methods of Study,* Ed. by L. M. Tocantins, Grune and Stratton, N. Y., 1955.

6. Rees, H. M., Ecker, E. E., *J.A.M.A.,* 1923, v80, 621.

7. Quick, A. J., *Am. J. Clin. Path.,* 1940, v10, 222.

8. Alexander, B., Goldstein, R., Landwehr, G., *J. Clin. Invest.,* 1951, v30, 252.

9. Cullen, E. G., Van Slyke, D. D., *J. Biol. Chem.,* 1920, v41, 587.

10. Swan, H., Virtue, R. W., Blount, S. G., Kircher, L. T., *Ann. Surg.,* 1955, v142, 382.

11. Helmsworth, J. A., Nat. Acad. Sci., *The Physiology of Induced Hypothermia,* Publ. 451, Washington, D.C., 1956, p197.

12. D'Amato, M. E., *ibid.,* p146.

13. Villalobos, T. J., Adelson, E., Riley, P., *ibid.,* p186.

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Potentiating Effects of Prenatal X-Irradiation on Dental Caries in the Rat.* (23690)

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It is well established that x-irradiation during the prenatal period will result in abnormalities or death of the young depending on the time of gestation and the dosage of x-irradiation administered. The pertinent literature in this field has been extensively reviewed by Russell(1). These studies, however, have dealt primarily with the effects of x-irradiation on the young as judged by their morphological appearance or viability at the time of parturition or the period immediately following. Comparatively few studies have been conducted to determine the effects of x-irradiation during prenatal life on the subsequent post-weaning response of the young. Growth retardation, brain damage and damage of the retina, cord and ganglia, sterility, skin defects and cataracts, and impaired maze learning performance(1-3) have been observed in the surviving young of mother rats administered sublethal doses of x-irradiation during various periods of pregnancy. In the present communication data are presented on the effects of x-irradiation during the formative period of tooth development (18th, 14th or 10th day of pregnancy) on susceptibility to dental caries in the rat.

Procedure. Forty female rats of the Long-Evans strain which had been raised from weaning on a natural food stock ration† were selected at 3 to 4 months of age and an average body weight of 188 g. Animals were divided at random into 4 equal groups of 10 rats each and were mated to males of proven fertility. Pregnancy was dated by the finding of sperm in the vaginal smear.‡ Animals in Group I served as non-irradiated controls; those in Groups II, III and IV received a single exposure of 150 r x-irradiation on the 18th, 14th or 10th day of pregnancy respec-

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† Rockland Rat Diet, Arcady Farms Milling Co., Chicago, Ill.