PRELIMINARY AND SHORT REPORT

STUDIES ON URTICARIA PIGMENTOSA: I. RELEASE OF A HEPARINOID MATERIAL INTO THE CIRCULATION FOLLOWING DIRECT STIMULATION OF URTICARIA PIGMENTOSA LESIONS*

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Urticaria pigmentosa (1) is an uncommon, chronic, inflammatory disease of the skin characterized histologically by localized deposits of mast cells in the corium and around the cutaneous appendages. Clinically it manifests itself by the appearance of pigmented macules and papules which wheal on stroking or other physical irritation.

It has been shown that the metachromatic granules contained in the mast cell cytoplasm consist of a heparinoid material which prolongs the clotting of blood *in vitro* (2, 3). However, most attempts to demonstrate any abnormal heparinoid activity in patients with urticaria pigmentosa have not met with success (3, 4), even though it has been repeatedly noted that these skin mast cells discharge their granules and lose much of their metachromasia after direct physical stimulation (5).

With the rationale that the demonstration of anticoagulant activity might occur only after maximal stimulation of all or most of the abnormal mast cell deposits, we have studied the coagulation mechanisms of eight such patients before and after whealing induced by brisk rubbing of the entire body surface with a rough towel. Our results suggest that the discharge of the mast cell granules is accompanied by an increase in the heparinoid titer of the subjects blood.

TABLE I

Methods used for study of coagulogram

Oil Clot Retraction Time	Hirschboek (6)	25–45 minutes
Prothrombin Consumption	Quick et al. (7)	Over 70% in 1 hr.
1-stage Prothrombin	Quick	100% of normal
Platelet Count	Rees & Ecker	200,000–300,000 cmm.
Heparin Titer	Allen et al. (8)	100–140 gamma protamine

METHOD

Eight patients with typical urticaria pigmentosa served as experimental subjects. Their ages ranged from one to forty-seven years. (Two adults and six children.) All had the typical history and physical findings of the disease. Biopsies of representative skin lesions were performed on all patients and confirmed the clinical impressions. A young adult physician with marked dermographism but no evidence of urticaria pigmentosa served as control.

The coagulation mechanisms of all patients were studied by means of the tests shown in Table I. The examinations were performed before and 20, 60, and sometimes 120 minutes after brisk rubbing of the entire body surface with a bath towel.

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TABLE II

Coagulation tests before and after stimulation in urticaria pigmentosa

Patient	Age (yrs)	Wheal Formation (+1–+4)	Tests	Time		
				0 min.	30 min.	120 min.
1. A. L.	47	4+	Clotting Time (min)	7.5	7.5	5.5
			Oil Clot Retraction Time (min)	30	29	29
			Prothrombin Consumption (%)	51	63	54
			1-stage Prothrombin (%)	85	85	87
			Platelet Count (thous./cmm)	329	302	351
			Heparin Titer (gamma protamine req'd)	80	180	100
2. M. C.	4	4+	Clotting Time (min)	8	16	5
			Oil Clot Retraction Time (min)	47	69	45
			Prothrombin Consumption (%)	81	79	53
			1-stage Prothrombin (%)	1000	—	100
			Platelet Count (thous./cmm)	257	292	273
			Heparin Titer (gamma protamine req'd)	100	160	100
3. D. C.	1	4+	Clotting Time (min)	4	8	
			Oil Clot Retraction Time (min)	29	30	
			Prothrombin Consumption (%)	77	79	
			1-stage Prothrombin (%)	100	—	
			Platelet Count (thous./cmm)	276	330	
			Heparin Titer (gamma protamine req'd)	160	240	
4. E. D.	20	0–1+	Clotting Time (min)	9.5	10	
			Oil Clot Retraction Time (min)	35	38	
			Prothrombin Consumption (%)	14	11	
			1-stage Prothrombin (%)	40	39	
			Platelet Count (thous./cmm)	218	222	
			Heparin Titer (gamma protamine req'd)	140	140	
5. P. N.	2.5	4+	Clotting Time (min)	5	8	3
			Oil Clot Retraction Time (min)	14	56	18
			Prothrombin Consumption (%)	69	71	78
			1-stage Prothrombin (%)	100	100	—
			Platelet Count (thous./cmm)	369	401	389
			Heparin Titer (gamma protamine req'd)	80	120	80
6. S. G.	7	4+	Clotting Time (min)	7.5	8	
			Oil Clot Retraction Time (min)	33	29	
			Prothrombin Consumption (%)	27	31	
			1-stage Prothrombin (%)	47	54	
			Platelet Count (thous./cmm)	307	304	
			Heparin Titer (gamma protamine req'd)	60	160	
7. A. S.	5	1+	Clotting Time (min)	10	8.5	
			Oil Clot Retraction Time (min)	31	32	
			Prothrombin Consumption (%)	78	77	
			1-stage Prothrombin (%)	100	100	
			Platelet Count (thous./cmm)	446	422	
			Heparin Titer (gamma protamine req'd)	120	120	

TABLE II—*Cont.*

Patient	Age (yrs)	Wheal Formation (+1–+4)	Tests	Time		
				0 min.	30 min.	120 min.
8. D. C.	6	3+	Clotting Time (min)	4	8	
			Oil Clot Retraction Time (min)	29	30	
			Prothrombin Consumption (%)	37.3	35.3	
			1-stage Prothrombin (%)			
			Platelet Count (thous./cmm)	276	330	
			Heparin Titer (gamma protamine req'd)	160	240	
9. J. L. (control)	34	3+	Clotting Time (min)	7	9	
			Oil Clot Retraction Time (min)	30	31	
			Prothrombin Consumption (%)	31	33	
			1-stage Prothrombin (%)	68	61	
			Platelet Count (thous./cmm)	445	431	
			Heparin Titer (gamma protamine req'd)	80	60	

RESULTS

All patients showed coagulation tests within normal limits before stimulation except for two with moderately prolonged 1-stage prothrombin times. Since the prothrombin consumption is expressed as the difference between the prothrombin activity of the plasma and of the serum, this resulted in a reduction of the prothrombin consumption in these two cases. One patient (Case 3) showed a slightly elevated heparin titer before stimulation.

Thirty minutes after stimulation only two patients showed a significant prolongation of their clotting time and the same two showed an increase of their oil clot retraction time. The latter test includes both the time necessary for clotting and for clot retraction so that the prolonged clotting time probably contributed in some measure to the increase. There was no change in the 1-stage prothrombin time, the prothrombin consumption nor in the platelet count. Six of the eight patients showed a significant rise in titrable heparinoid activity of their blood. In the three cases in which tests were carried out two hours after stimulation, all changes had disappeared. No abnormalities were found in the coagulogram of the control either before or after stimulation. (Table II)

DISCUSSION

As can be seen in Table III, six of the eight patients studied showed an increase in the titrable serum heparin level. The two negative results were in cases with mild forms of the disease where no whealing was noted after stimulation.

TABLE III

Heparin titer before & after stimulation (gamma protamine)

Patient	0 Min.	30 Min.	120 Min.
A. L.	80	180	100
M. C.	100	160	100
D. C.	160	240	—
E. D.	140	140	—
P. N.	80	120	80
S. G.	60	160	—
A. S.	120	120	—
D. C.	160	240	—
J. L. (control)	80	60	—

Until recently, the main criterion of the heparinoid activity of the blood was considered to be the clotting time. Using this criterion, it can be seen that little change takes place in our patients after brisk stimulation (two of eight cases). However, the clotting time is a rough test and will not reflect relatively minor changes in heparinoid activity. Although methods of varying degrees of complexity have been proposed to demonstrate abnormal heparinoid states, the protamine titration used in our experiments is simple to carry out and requires a minimum of apparatus.

One of us (W. N. B.) has recently reported that the changes in the coagulation mechanism which accompanied the administration of commercial heparin to rabbits and man consists of a prolongation of the clotting and oil clot retraction times, reduction in the prothrombin consumption and elevation of the heparin titer (9). Only two of our patients showed changes in the clotting and oil clot retraction times and none showed the characteristic changes in the prothrombin consumption. The cause for the failure of these changes to appear in our cases is unknown, but it must be emphasized that little is known about the chemical similarities of commerical heparin and the heparinoid material liberated in urticaria pigmentosa patients. From the apparent brevity of the heparin titer elevation, it can be suggested that the effect of physical stimulation on the mast cells acted more like an "intravenous" injection of commercial heparin than an "intramuscular" injection. This is to be expected in view of the observed perivascular location of such cells in the sub-cutaneous tissue.

SUMMARY

1. An increase in the titrable heparinoid activity of serum has been demonstrated in six of eight patients with urticaria pigmentosa following brisk generalized rubbing with a towel. The two failures were patients who had a mild form of the disease and did not show whealing after stimulation.

2. The increase in heparinoid titer lasted only a short time and was not accompanied by changes in the oil clot retraction time and prothrombin consumption usually seen following injections of commercial heparin. The reason for this is unknown.

3. It is suggested that the abnormal mast cells in urticaria pigmentosa contain a heparinoid material which is discharged into the circulation in small quantities after physical stimulation of the lesions.

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