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Studies on relationship between serum properdin and cancer II. Studies on the serum properdin levels of tumor bearing animals and patients with malignant tumors

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Studies on relationship between serum properdin and cancer II. Studies on the serum properdin levels of tumor bearing animals and patients with malignant tumors*

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Abstract

1. The properdin levels in sera from mice bearing Ehrlich ascitic carcinoma and from rabbits with Brown-Pearce carcinoma decrease inversely with the increase of the ascites or the tumors. In the incipient period of tumor transplantation, the level rather rises. When the tumor is proliferating or large, the level keeps falling or is low. On the contrary, when the tumor is regressing or disappears, the level elevates or reverts to that before transplantation. Strong A and R III mice with spontaneous mammary cancer have markedly low serum properdin levels as compared with those of healthy mice. 2. The properdin levels are less than 2 units per milliliter of the serum in 44.4 per cent of patients with gastric cancer, in 18.2 per cent of ones with non-malignant tumor and in 18.2 per cent of ones with gastric or duodenal ulcer. The abnormal low level has been found in 33.3 per cent of patients without recurrence, who had undergone extended radical gastrectomy combined with radical lymphadenectomy for gastric cancer. 3. Some correlation can be seen between the serum properdin levels and the degree of progress of gastric cancer. 4. The cancer patients with low total serum protein have lower serum properdin levels than those having nomal protein. 5. As for influence of surgical operation on the serum properdin levels, there is observed a tendency that a minor operation causes the levels to increase and a major operation causes the levels to fall. 6. It has been inferred that the properdin system could be one of the host natural resistance against cancer.

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STUDIES ON RELATIONSHIP BETWEEN SERUM PROPERDIN AND CANCER

II. STUDIES ON THE SERUM PROPERDIN LEVELS OF TUMOR BEARING ANIMALS AND PATIENTS WITH MALIGNANT TUMORS

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Roughly speaking there are two cures for diseases. One is to eliminate the cause of diseases positively from outside and the other is to increase the power of resistance that individuals have.

In the majority of individuals various kinds of infection and other injuries can be overcome with defense mechanisms with which they are naturally provided.

Recently the resistance of a human body is often neglected because of notable development of chemotherapy in infectious diseases and in cancer, likewise, the body resistance has come to be like a neglected child with the remarkable development of surgery and with the advent of many anticancer agents. However, it will take a long time before anticancer agents display the same power against cancer as chemotherapy against infectious diseases. Now that operations to stamp out cancer surgically have come to a limit and the existence of specific immune antibody for cancer is doubtful, it is not without reason that we need reappraisal of nonspecific immune antibody.

Among natural defense mechanisms, it is well known that there are white blood corpuscles, phagocytic action and so on, in cellular resistances.

Humoral defense mechanism was reported by LANDOIS[1] in 1875, and the existence of agglutinins and lysis for bacteria in serum became clear, and it is now thought that these might have some relation to complement or to components of complement[2,3]. In 1910 FREUND and KAMINER[4] discovered that serum of healthy persons contains a certain substance that can destroy human cancer cells. In 1954 PILLEMER *et al.*[5] discovered one new serum protein, properdin, while trying to separate the third component of complement. This is a powerful factor of natural resistance and offered a clue to explain natural defense mechanisms. In 1957, SOUTHAM *et al.*[6,7] reported that homotransplantation of

human cancer cells is possible to cancer patients who have little serum properdin, but it is not to healthy persons who possess considerable properdin, and there is not appreciable difference between the former and the latter except in properdin levels.

It is now believed that this may be natural resistance to cancer, but owing to the difficulty in its assay, it has not been thoroughly investigated. Concerning the relationship between transplantable tumor and serum propeadin levels in tumor bearing animals there is only a brief report by HERBUT *et al.*[8] In this paper the author describes about his attempts to investigate what influence the growth of transplanted tumor has on serum properdin levels in tumor bearing animals and next, chiefly in stomach cancer of human, whether there is any difference between the serum properdin level in patients with malignant tumor and that in non-malignant tumor, and whether there is any relation between the development of the stomach cancer and properdin levels, and how the properdin level is altered by the postoperative conditions of patients.

MATERIALS AND METHODS

The experimental animals used were 24 comparatively young adult rabbits, weighing approximately 2 kg, and 60 mature female Cb strain mice, weighing about 20 g. and Strong A and R III mice bearing the spontaneous mammary cancer, 3 in each and 3 pair fed controls. The animals were placed on definite diet for a week before the use. The experimental tumors transplanted were Brown-Pearce carcinoma for rabbits and Ehrlich ascitic carcinoma for mice.

Brown-Pearce carnioma was transplanted into the rabbit posterior thigh muscles, and the transplant was gouged aseptically 3 weeks after transplantation. The fresh tumor tissue so obtained was put in homogenizer excluding its necrotic parts, minced gently, and made into suspension of 4 or 5 volumes with physiological saline solution. Each 0.3 ml of this suspension was given to one animal.

The rabbits were divided into 4 groups; Animals belonging to Group I received bilateral injection of the suspension into posterior thigh muscles. In the animals belonging to Group II the suspension was injected into liver after opening the abdominal cavity by the upper midline incision. In the animals of Group III the suspension was injected into the portal vein after opening the abdominal cavity as those in Group II. In those of Group IV the suspension was injected into the posterior thigh muscle.

Before and after tumor transplantation the blood of each rabbit was taken several times periodically. Selecting the time when they were hungry, approximately 1 ml of the blood taken from the marginal vein of ear was allowed to

clot at room temperature for 2 hours.

The serum was separated by centrifugation for 15 minutes at 4000 r. p. m. and recentrifuged. These sera were stored at −30°C in the sealed tubes. After finishing the blood collection of each series, properdin levels of all the samples were measured simultaneously.

Rp and R_3 prepared from guinea-pig sera were employed.

Ehrlich ascitic carcinoma which developed in the abdominal cavity of mice was taken through capillary tubes. 0.2 ml of 7 to 10 day old ascites containing 5 to 10 million cancer cells diluted with saline solution was transplanted into the abdominal cavity of each mouse.

Before and after tumor transplantation, 0.5 ml of the blood was taken from 3 or 4 mice by means of cardiac puncture periodically.

The separated sera were pooled to yield a single serum specimen and preserved at −30°C till all the samples were ready.

Rp and R_3 prepared from guinea-pig sera were used for properdin assay.

Sixty female Cb strain mice were divided into three groups of 20 mice each. The ascitic carinomas from different mice were transplanted into the abdominal cavity of each group at different time.

In the patients bearing tumor blood was taken from the elbow veins, early in the morning before taking food in those in hospital, and before lunch in those of out-patients. The serum properdin levels were measured the day after the separation of serum, or separated serum was stored at −30°C in the sealed vessels for further use. Rp prepared from sera of cancer patients and R_3 made of guinea-pig sera were used.

The foregoing manipulation was performed as aseptically as possible. The method of properdin assay was described precisely in Part 1. The properdin levels of all the samples in the same series were measured with the same reagents on the same day.

RESULTS

In 10 rabbits of Group I the transplanted tumor grew in about a week after transplantation to the size of a little finger and in most of the cases it progressively grew to the size of a pigeon egg in about 2 weeks, to a small hen-egg size in about 3 weeks, and then the rabbits died in the state of cachexia. As shown in Fig. 1, serum properdin levels tended to fall with the aggravation of tumor, but a significant relation could not be seen between the number of days from transplantation to death and the rate of fall of properdin levels. In one case of natural healing in this group (Fig. 1, △), the tumor was palpable a week after transplantation, but gradually regressed later. The affected locus was ope-

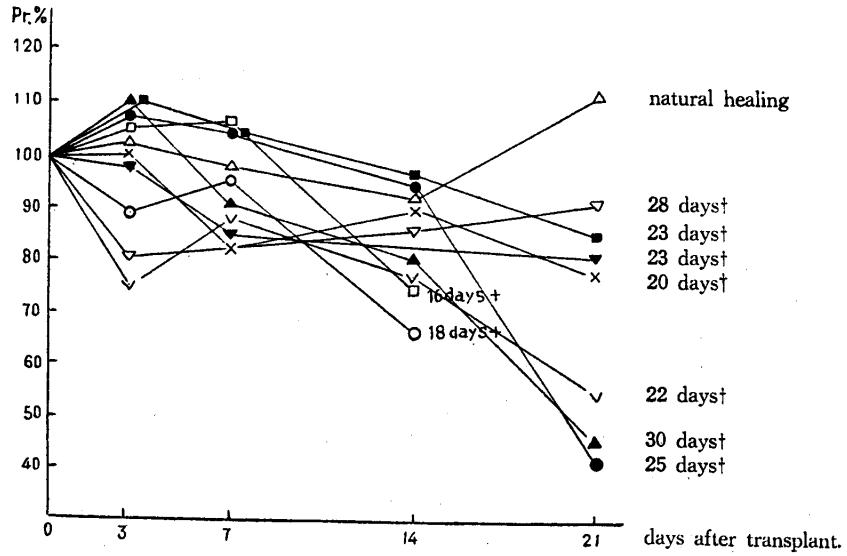

Fig. 1. Change of properdin levels in rabbits with Brown-Pearce carcinoma into posterior thigh muscles.

rated upon 40 days later, but tumor tissue could not be detected. In such a case, properdin level, as if it had shared the fate of tumor, indicated only a transitory fall in a week and gradually rose and then reverted to the level before transplantation.

In 7 rabbits of Group II a decrease in weight and the lack of appetite were found on the seventh day after transplantation.

Owing to the multiple growth of tumor all over the liver, they all died within about 2 weeks with the sudden increase of cachexia and hemorrhagic ascites. Serum properdin indicated rather high levels 3 days after transplantation, but began to fall in a week and fell rapidly 3 or 4 days before their death (Fig. 2). One case in this group (Fig. 2, ×) indicated a little decrease of appetite 8 days after transplantation, but soon recovered and seemed to have been healed naturally without any signs of the decrease in weight and cachexia, but after 14 days it began to languish rapidly and after 18 days died of tumor. The liver swelled more than three times the original to 270 g (normally the average weight of 10 rabbits is 51 g). There could be seen hardly any parenchyma in the liver which was occupied by the numerous whitish tumors, the size of a rice grain and the accumulation of hemorrhagic ascites could be seen. Serum properdin levels changed parallel with growth of the tumor, and rose transitorily about 2 weeks after transplantation and then fell suddenly, on the day before death the level was one fifth that before transplantation.

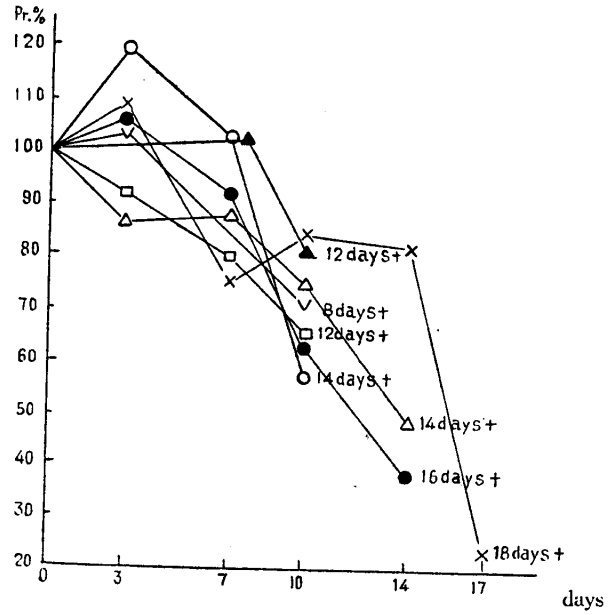

Fig. 2. Change of properdin levels in rabbits with Brown-Pearce carcinoma transplanted into liver.

In 3 rabbits of Group III, properdin levels reverted to the value before operation one week after laparotomy and tended to rise a little in 2 weeks (Fig. 3).

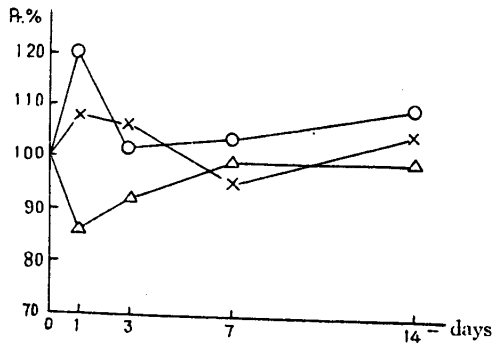

Fig. 3. Change of properdin levels in rabbits undergone a simple laparotomy.

In 4 rabbits of Group IV two cases of rabbits whose tumor grew very big and occupied the whole of their posterior thigh muscle were laparotomized 2 weeks and 3 weeks after transplantation. The venous blood which returned from the thigh with tumor and the healthy one was taken separately from each *v. ilica externa*, the arterial blood was taken from *a. ilica communis*, and then properdin level of each blood was measured. There was no significant difference between each serum properdin level (Table 1).

Table 1.

No. of rabbit	Properdin titer of arterial blood (units/ml.)	Properdin titer of venous blood from side with tumor	Properdin titer of venous blood from healthy side
11 after 2 weeks	6.6	6.5	6.1
14 after 3 weeks	5.1	4.6	5.4

In the mice transplanted with Ehrlich ascitcs carcinoma all the animals showed the swelling of the abdomen in 4 or 5 days after transplantation and their weights increased remarkably, and all the mice died of tumor. Fifty per cent of them were alive for two weeks or so, and almost all animals died within 7 to 20 days. Serum properdin, as could be seen in Fig. 4, fell in inverse proportion to the aggravation of tumor and the increase in weight. For one or two days after transplantation it indicated rather higher level than before transplantation, but in 3 to 6 days suddenly it fell to approximately one half the level before transplantation and then it gradually decreased and could not be detected before death of mice.

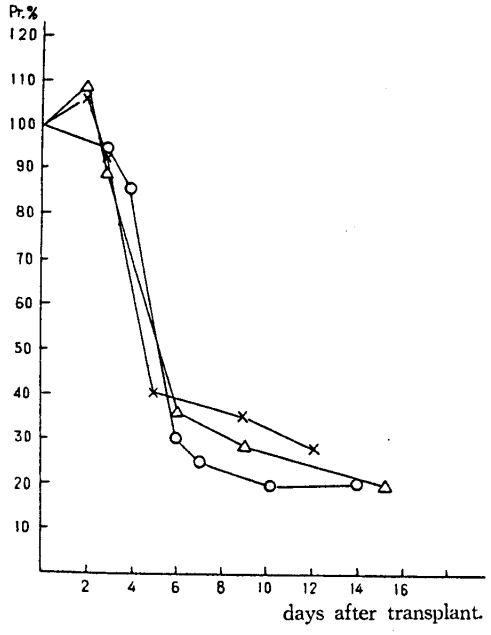

Fig. 4. Change of properdin levels in mice with Ehrlich ascites carcinoma.

In Strong A and R III strain mice with spontaneous mammary cancer the serum properdin levels of tumor bearing mice fell one fifth to one tenth of the levels of healthy mice(Table 2).

Table 2.

	Properdin titer in mice with mammary cancer (units/ml.)	Properdin titer in healthy mice
Strong A mice	1.0	9.4
RIII mice	2.2	8.9

The serum properdin levels of patients with malignant tumor were found to be less than 2 unts per milliliter of serum in 20 cases of 45 patients (Table 3).

Among them, the level was less than 2 units in 13 cases of 25 with stomach cancer, in 2 cases of 6 with colon cancer, in 2 cases of 5 with mammary cancer, in one of 3 with cerebral tumor.

The stomach cancer may be classified according to its progress of liver metastasis, lymphatic metastasis, peritoneal dissemination, infiltration in stomach serosa and expressed respectively with H, L, P, S, and according to the extent of them from what is mild to what is serious as H_0, H_1, H_2, H_3, L_0—L_4, P_0—P_4 and S_0—S_4. Types of cancer are expressed by the classification of BORRMANN[14].

As shown in Tables 3 and 4, the properdin level tended to fall in advanced cancer.

In 6 cases out of 33 patients having no malignant tumor the properdin level was less than 2 units (Table 5). Among them, it was so in 2 of 11 suffering from gastric or duodenal ulcer, and none of 5 cases of chronic mastitis and mammary fibroadenoma showed abnomal level.

The effect of operative injury on properdin level was observed. The properdin levels were measured before and after operation, in the 7 cases where gastrojejunostomy was performed by means of Billroth II method after the operation of gastrectomy combined with radical lymphadenectomy for gastric cancer, in 3 cases of gastric ulcer and in one case of gastric polyp where gastroduodenostomy was performed by Billroth I method and in cases of other diseases.

In the case of gastric cancer where the extensive radical operation was performed, in 2 to 3 weeks after operation the level seldom reverted to that before operation, but in the case of gastric ulcer, gastric polyp where gastrectomy alone was performed, the level rather tended to rise after operation as in Fig. 5. In mammary cancer in which radical mastectomy was performed, in about 2 weeks after operation the level reverted to that prior to operation. In appendicitis and inguinal hernia in which operative injury was slight, the level hardly changed and in 2 cases of cerebral tumor where craniotomy with extirpation of tumor had been performed, the level rose considerably after operation (Fig. 6).

The changes were observed in serum properdin levels after extensive radical operation for gastric cancer, which means total removal of visible lymphnodes.

Properdin and complement are measured about a month after the radical operation just before their discharge from hospital in 4 cases, and 4 months, one year, 2 years, and 3 years after the radical operation in 15 cases. Among

Table 3.

No.	Age	Sex	Malignant tumor diesease	Properdin (units/ml.)			
				≦2	2—4	4—6	6≦
1	62	♂	Gastric cancer (II $H_0P_3L_3S_3$)	•			
2	64	♂	Recurrence of gastric cancer	•			
3	58	♂	Gastric cancer with liver metastasis		•		
4	65	♂	Recurrence of gastric cancer		•		
5	52	♂	Gastric cancer (II $H_3P_0L_3S_2$)	•			
6	56	♂	Gastric cancer (IV $H_0P_3L_3S_3$)	•			
7	48	♂	Gastric cancer (IV $H_0P_0L_2S_1$)			•	
8	35	♀	Gastric cancer (IV $H_0P_4L_3S_4$)	•			
9	64	♂	Gastric cancer (IV $H_0P_0L_3S_4$)	•			
10	62	♂	Gastric cancer (II $H_0P_3L_4S_4$)			•	
11	61	♂	Gastric cancer (II $H_0P_3L_4S_1$)	•			
12	60	♂	Gastric cancer (III $H_0P_0L_2S_3$)		•		
13	73	♂	Gastric cancer (I $H_0P_0L_2S_1$)	•			
14	42	♂	Gastric cancer (III $H_0P_4L_3S_4$)	•			
15	67	♂	Gastric cancer (II $H_0P_0L_3S_1$)		•		
16	67	♂	Gastric cancer (II $H_0P_0L_2S_0$)				
17	55	♂	Gastric cancer (III $H_0P_0L_2S_2$)	•			•
18	54	♀	Gastric cancer (III $H_0P_0L_1S_3$)				•
19	49	♀	Gastric cancer (IV $H_0P_0L_2S_2$)			•	
20	63	♂	Gastric cancer (II $H_0P_0L_1S_2$)	•			
21	71	♂	Gastric cancer (II $H_0P_0L_3S_3$)	•			
22	63	♂	Gastric cancer (III $H_0P_0L_2S_2$)			•	
23	55	♂	Gastric cancer (I $H_0P_0L_1S_0$)		•		
24	50	♂	Gastric cancer (II $H_0P_0L_3S_4$)	•			
25	40	♂	Gastric cancer (III $H_0P_0L_3S_1$)			•	
26	74	♂	Rectum cancer		•		
27	56	♀	Rectum cancer		•		
28	68	♀	Rectum cancer	•			
29	63	♂	Rectum cancer			•	
30	74	♂	Colon cancer	•			
31	54	♂	Rectum cancer		•		
32	72	♀	Mammary cancer				
33	40	♀	Mammary cancer	•	•		
34	47	♀	Mammary cancer		•		
35	41	♀	Mammary cancer		•		
36	46	♀	Mammary cancer	•			
37	42	♀	Meningioma		•		
38	33	♀	Acoustic tumor		•		
39	32	♂	Hypophysial duct tumor	•			
40	62	♂	Cancer of mouth floor	•			
41	26	♂	Seminom with metastasis		•		
42	32	♀	Lymphosarcoma			•	
43	42	♂	Sarcoma		•		
44	50	♂	Liver cancer with lung metastasis	•	•		
45	53	♂	Lung cancer				

Red cells	White cells	Total serum protein	Liver function (B. S. P.)	Sedimentation rate of red cells
432×10⁴	5500	5.8 g/dl	15—5% (30′—45′)	45—95 (1—2 h.)
342×10	4400	6.2	10—7.5	15—39
358×10	3800	7.1	20—15	16—43
312×10	7000			5—18
168×10	4600	5.5	17.5—12.5	70—115
450×10	6100	5.8	7.5—2.5	10—25
515×10	7000	6.7		15—28
366×10	6400	6.7	2.5—0	18—30
295×10	5800	6.0	5—2.5	25—46
368×10	7200	5.9	7.5—5.0	42—77
435×10	9400	7.0	27.5—20	41—82
332×10	7600	6.2	5—2.5	60—95
350×10	7200	5.5	15—10	15—35
428×10	5400	5.0		5—20
268×10	6400	6.0	12.5—10	20—42
269×10	6500	6.1	2.5—0	58—83
420×10	7800	7.0	5—2.5	7—18
352×10	5800	5.6	2.5—0	9—25
	4800	6.3	7.5—2.5	
	7400	5.3	5—2.5	
	4000	5.5	12.5—7.5	
360×10	6600	6.7	5—0	3—7
	5200	6.8	10—7.5	5—12
191×10	3200	5.4	15—5	100—108
346×10	6200	7.0	5—2.5	10—15
325×10	5900			
405×10	5400	6.4		10—34
351×10	4200	5.5	17.5—15	27—66
395×10	4900	5.2		10—20
420×10	5400	5.8	10—5	
470×10	6500	7.5	15—12.5	40—70
396×10	5600	6.0		5—24
498×10	4300	7.0	10—5	28—60
359×10	7800	5.6	2.5—0	4—17
430×10	5000	6.8		9—25
440×10	5300	6.4	7.5—2.5	10—28
330×10	6800	7.0		10—20
320×10	1200	6.0	15—10	35—45
468×10	10200			
412×10	8200	6.7	22.5—20	14—30

Table 4. a. Serum properdin levels and extent of metastasis to the lymphnodes.

Metastasis to lymphnodes	Properdin (unit/ml.)	
	≦2	2<
L_0		
L_1	1	2
L_2	2	5
L_3	8	2
L_4	1	1

b. Serum properdin levels and extent of infiltration to stomach serosa.

Infiltration to stomach serosa	Properdin (unit/ml.)	
	≦2	2<
S_0		2
S_1	2	3
S_2	3	2
S_3	3	2
S_4	4	1

c. Serum properdin levels and extent of dissemination to peritoneum.

Dissemination to peritoneum	Properdin (unit/ml.)	
	≦2	2<
P_0	7	9
P_1		
P_2		
P_3	3	1
P_4	2	

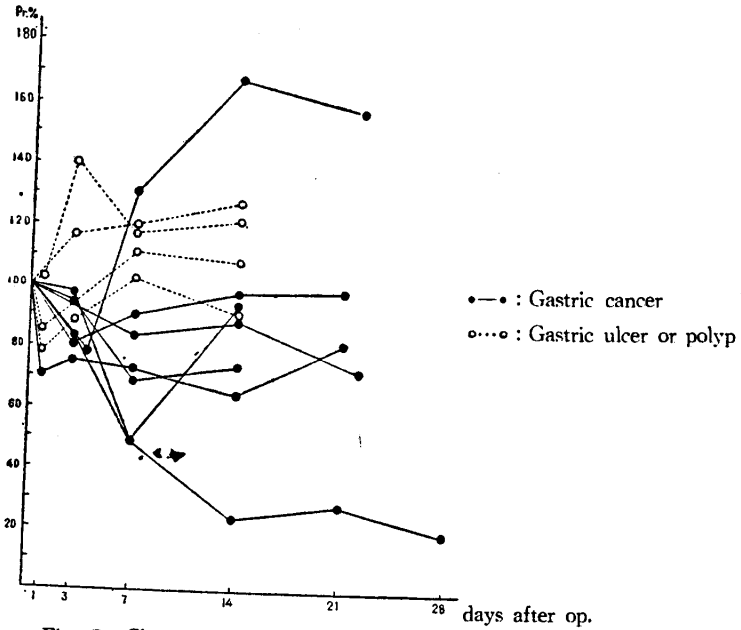

Fig. 5. Change of properdin levels in postoperative patients.

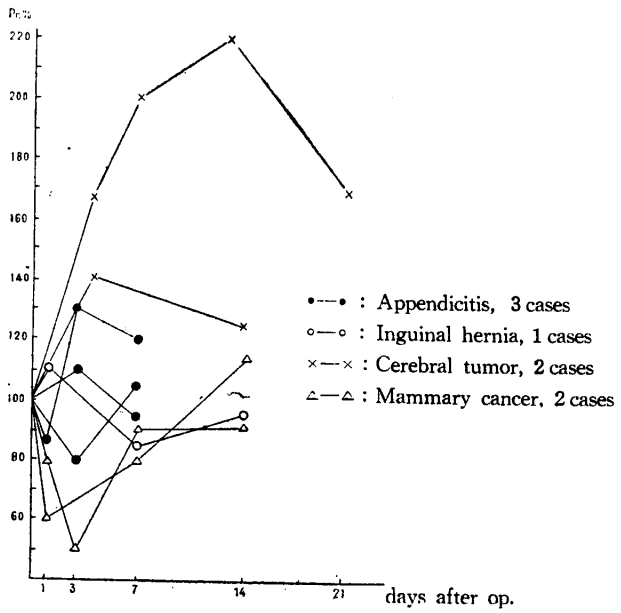

Fig. 6. Change of properdin levels in postoperative patients.

Table 5.

No.	Age	Sex	Non malignant tumor disease	Properdin (units/ml.)			
				≦2	2—4	4—6	6≦
1	42	♂	Duodenal ulcer			•	
2	49	♂	Gastric ulcer		•		
3	48	♂	〃				•
4	63	♀	〃		•		
5	21	♂	〃			•	
6	25	♂	Gastroduodenal ulcer	•			
7	37	♂	Gastric ulcer				•
8	25	♂	〃	•			
9	57	♂	〃			•	
10	23	♂	〃				•
11	47	♂	〃			•	
12	48	♀	Gastroptosis	•			
13	45	♀	〃			•	
14	11	♂	Acute appendicitis	•			
15	21	♂	〃			•	
16	34	♂	〃			•	
17	27	♀	Gastroptosis		•		
18	23	♀	Chronic mastitis			•	
19	39	♀	〃				•
20	28	♀	〃			•	
21	29	♀	〃			•	
22	43	♀	Mammary fibroadenoma				•
23	44	♀	Gastropolyp			•	
24	62	♂	Rectumpolyp		•		
25	66	♂	Hernia sacrotalis dextra		•		
26	3	♀	Hernia ext. ing. sinistra		•		
27	29	♂	Lumbar prolapsed disc				•
28	41	♂	〃				•
29	27	♂	Cerebrale arachnoiditis				•
30	43	♂	〃			•	
31	39	♀	〃			•	
32	40	♂	Thromboangitis obliterans	•			
33	48	♂	Haemorrhoid	•			

them were two patients, who had received the radical operation under the diagnosis of gastric cancer and proved to be gastric ulcer from the histological examination after the operation.

In 7 cases out of 19, the properdin level was less than 2 units, and with the exception of the cases of recurrence and of ulcer, the level was the same in

Red cells	White cells	Total serum protein	Liver function (B. S. P.)	Sedimentation rate of red cells
348×10⁴	4800	7.2g/dl	10—5% (30′—45′)	7—22 (1—2h.)
380×10	7200	7.6	12.5—7.5	4—5
360×10	6900	7.1	5—2.5	2—5
257×10	5000	7.0	7.5—2.5	
381×10	6200			
501×10	8200	7.0	5—2.5	6—13
376×10	7000	6.8		10—18
360×10	4600	7.0	8.5—2.5	20—50.5
514×10	7200	7.0	2.5—0	1—2
425×10	5400	6.0	10—7.5	3—9
307×10	4800	7.0	5—0	10—22
320×10	5400	7.5	15—12.5	16—23
394×10	6200	7.0	5—2.5	5—15
408×10	8400	6.5	10—5	5—12
380×10	6400	6.0	5—0	7—20
482×10	12000	6.6	5—2.5	
425×10	8800			
421×10	5600		15—10	3—7
514×10	7200	7.0	2.5—0	1—2
497×10	7600			

5 cases out of 15. No significant relations could be seen between the titer of serum complement and components of serum complement and properdin level. The properdin levels showed a tendency to become abnormally lower in patients over 2 years after operation (Table 6).

The relationship between serum properdin level and total serum proteins

Table 6.

No.	Age	Sex	Type, Gastric cancer	Time after operation	Properdin (unit/ml.)			
					≦2	2—4	4—6	6≦
1	63	♂	II ($H_0P_0L_1S_2$)	20 days	•			
2	60	♂	III ($H_0P_0L_2S_3$)	20 〃		•		
3	62	♂	II ($H_0P_3L_4S_4$)	30 〃	•			
4	73	♂	I ($H_0P_0L_2S_1$)	30 〃		•		
5	59	♂	II ($H_0P_0L_2S_2$)	4 months			•	
6	55	♂	II ($H_0P_0L_2S_1$)	4 〃	•			
7	64	♂	IV ($H_0P_0L_3S_4$)	7 〃	•			
8	49	♂	III ($H_0P_0L_2S_0$)	8 〃				•
9	45	♀	IV ($H_0P_0L_1S_0$)	9 〃			•	
10	54	♂	III ($H_0P_0L_2S_1$)	1 year		•		
11	48	♂	IV ($H_0P_0L_3S_0$)	1 〃			•	
12	62	♂	III ($H_0P_0L_1S_0$)	1 y. 8 m.		•		
13	31	♂	Gastric ulcer	2 year				•
14	51	♂	〃	2 y. 1 m.			•	
15	60	♂	III ($H_0P_0L_2S_2$)	2 y. 3 m.	•			
16	55	♂	II ($H_0P_0L_2S_1$)	2 y. 6 m.		•		
17	54	♂	III	3 y. 3 m.	•			
18	43	♂	III	3 y. 6 m.		•		
19	56	♂	II	3 y. 6 m.	•			

Table 7. Serum properdin levels and serum total protein values.

Total protein gm/100 ml	Properdin (unit/ml.)	
	≦2	2<
4.0—5.0	1	
5.1—6.0	12	5
6.1—7.0	6	11
7.1—		2

has been observed. As in Table 7, low properdin level could be seen in many cancer patients with low total protein. No significant relation could be recognized among the number of white blood corpuscles, that of red blood corpuscles and liver function.

Complement and components of complement					Red cells	White cells	Total serum protein	Liver function (B. S. P.)	Sedimentatoin rate of red cells
C′	C'_1	C'_2	C'_3	C'_4					
4×	128×	8×	8×	128×	297×10⁴ 432×10	7000 7400	5.5	10—7.5% (30′—45′)	
8×	128×	16×	8×	128×	275×10	7200	6.8	30—30	3—10
8×	256×	16×	16×	128×	415×10	8000	7.6	12.5—7.5	8—24
8×	128×	8×	32×	256×	342×10	4400	6.2	10—7.5	15—36
4×	128×	8×	32×	256×	370×10	5800	7.5	5—2.5	
8×	128×	8×	16×	128×			6.5	5—2.5	11—21
8×	64×	8×	8×	128×	335×10	8006	8.1	10—5	9—25
16×	64×	16×	32×	256×	275×10	5800	6.2	30—20	19—36
8×	32×	8×	16×	64×	350×10	5200	6.5	12.5—10	18—43
8×	256×	16×	32×		470×10	6800	6.9	7.5—2.5	14—17
8×	128×	16×	32×	256×	385×10	12000	6.3	10—5	16—41
2×	16×	2×	8×	128×	455×10	6400	6.3	7.5—5	11—45
4×	64×	8×	32×	128×	300×10	7400	6.9	7.5—5	3—19
8×	128×	8×	8×	128×	335×10	5400	8.0	7.5—5	6—18
8×	64×	8×	16×	128×	365×10	8400	6.8	7.5—5	4—10
4×	128×	8×	8×	256×	410×10	5200	7.0	7.5—5	7—18

COMMENT

It has been clarified that there is some correlation between serum properdin and the spread of Brown-Pearce carcinoma in rabbits, Ehrlich ascitic carcinoma in Cb strain mice and spontaneous mammary cancer in strong A and R III strain mice. In the incipient stage of the spread of transplanted tumor, properdin level rather rises as if to check the spread, and when the ballance between properdin and tumor is broken and the growing power of tumor overcomes properdin level, tumor continues to aggravate and properdin level seems to fall inversely. When Brown-Pearce carcinoma is transplanted into the liver of rabbit, the fall of properdin is very notable as compared with the one transplanted into the thigh muscle, which seems to represent the function of the liver as the place producing properdin. In the fourth group of rabbits a significant difference can not be perceived between the properdin level of the blood from the thigh with tumor and that of healthy thigh, which shows that serum properdin might not be affected by tumor tissue itself, or be affected little, if any. It is said that when Ehrlich ascitic carcinoma is transplanted into abdominal cavity of mice, cancer cell division reaches its peak in 3 and 5 days after trans-

plantation. As if the growing power of the cancer cells has overcome properdin level and then cancer cells continue to divide, properdin suddenly decreases in 3 to 6 days after transplantation, which is a quite attractive phenomenon.

Concerning the serum properdin level of cancer patient, HINZ[10] reported that serum properdin level was nomal in patients with malignant tumor, but many other investigators[7,11,12,13] found that properdin levels fell abnormally in many cases of these patients, but reports on the relation between the progress of cancer, its metastasis and operative invasion and serum properdin levels are only few in number. In our department we have performed gastrectomy combined with radical lymphadenectomy for patients with stomach cancer and obtained satisfactory results and for the last ten years we have been continuing the researches on the metastasis of stomach cancer.

Among the patients with malignant tumor there were notably many cases with abnormally low properdien level as compared with non-malignant tumor patients and normal persons. With regard to operative injury and serum properdin level, there is a report[15] claiming that there is no significant relation between the former and the latter owing to a great deviation of the properdin level, but in the present work it was found that a slight operative injury caused properdin to rise and a severe injury caused properdin to fall.

It can be said that, though craniotomy with tumor-exstirpation is a great injury, the fact that properdin level rises a great deal after the operation seems to correspond to Hoff's report[16]. Hoff states that the center of nonspecific defense mechanism exists in the interbrain and reports that properdin rises if air is injected into the ventricle. ROTTINO *et al.*[12] as well as myself reported that properdin level was low in patients with low total serum protein.

The evidence that properdin may have a power to interrupt the progress of cancer or to inhibit the carcinogenesis can be obtained by taking out a great guantity of properdin and administering it to cancer bearing individuals, or those that are doomed to be attacked by cancer.

But it is difficult to prepare pure properdin and human beings require a great quantity of it. Properdin being a high molecular weight protein[5,17] has antigenic action[18], and thus it would be difficult to administer it to an animal of different species.

HERBUT[19] inferred that, in the heterotransplantation of transplantable human carcinoma of the colon (HR132) in Wister rats, the fact that the rate of tumor "takes" rose in the case of administering cortisone, total body irradiation and in the case of injecting a great quantity of zymosan, would be probably because of fall in the properdin level.

Later HERBUT *et al.*[20] said that properdin did not affect the rate of tumor "takes", and HUBEY *et al.*[21] claim that antitissue antibody has no bearing on

properdin in his study of a rabbit skin homografts.

SOUTHAM *et al.*[7] reported in their homotransplantation studies with cultivated human cancer cells that many examples of success in transplantation can be seen in advanced cancer patients with a considerable fall in properdin.

Thus contradictory reports appear perhaps because these workers do not take into consideration such factors as species antibody, histocompatibility and so on. In lymphosarcoma 6C3HED in C3H mice, HERBUT *et al.*[8] saw that, when tumor was growing or was large, serum properdin level fell, and when it was regressing or disappeared completely, the level was normal or rather higher.

It is now well known that the serum properdin levels from tumor bearing animals vary inversely with the growth of tumors and, in stomach cancer, there are many patients with low serum properdin level, and that in mice bearing spontaneous mammary cancer and human cancer properdin is much lower as compared with that of healthy ones or patients with non-malignant tumor.

Concerning the cytolysis of cancer cells *in vitro* by a normal human serum, FREUND and KAMINERS[4] report that, in abnormal serum or those which are destitute of properdin, cytolysis of cancer cells does not take place —these views indicate that there exists humoral natural immune antibody including properdin system for cancer as well as for bacteria, virus and protozoa.

The reason why properdin level is low in cancer patients is probably due to the fact that cancer cells themselves absorb properdin, or that cancer tissue polysaccharides, which combine with properdin to interfere with zymosan assay, are released in the blood stream, or that toxin injures the sites producing properdin, or that metabolic system including pantothenic acid[22] may be disturbed, or that these four coordinating with one another lower the properdin level.

CONCLUSIONS

1. The properdin levels in sera from mice bearing Ehrlich ascitic carcinoma and from rabbits with Brown-Pearce carcinoma decrease inversely with the increase of the ascites or the tumors. In the incipient period of tumor transplantation, the level rather rises. When the tumor is proliferating or large, the level keeps falling or is low. On the contrary, when the tumor is regressing or disappears, the level elevates or reverts to that before transplantation. Strong A and R III mice with spontaneous mammary cancer have markedly low serum properdin levels as compared with those of healthy mice.

2. The properdin levels are less than 2 units per milliliter of the serum in 44.4 per cent of patients with gastric cancer, in 18.2 per cent of ones with non-malignant tumor and in 18.2 per cent of ones with gastric or duodenal

ulcer. The abnormal low level has been found in 33.3 per cent of patients without recurrence, who had undergone extended radical gastrectomy combined with radical lymphadenectomy for gastric cancer.

3. Some correlation can be seen between the serum properdin levels and the degree of progress of gastric cancer.

4. The cancer patients with low total serum protein have lower serum properdin levels than those having nomal protein.

5. As for influence of surgical operation on the serum properdin levels, there is observed a tendency that a minor operation causes the levels to increase and a major operation causes the levels to fall.

6. It has been inferred that the properdin system could be one of the host natural resistance against cancer.

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