STUDIES ON THE INHIBITION OF PROTEOLYTIC ENZYMES BY SERUM

III. Physiological Aspects of Variations in Proteolytic Inhibition. The Concurrence of Changes in Fibrinogen Concentration with Changes in Trypsin Inhibition

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The antiproteolytic activity of serum, and its changes in association with disease are little understood in spite of the extensive work that has been done in this field. The increase in inhibition by serum during various disease states has been repeatedly studied since the original observation of Ascoli and Bezzola in 1903 (1) (reviews, 2, 3). Trypsin has been the enzyme usually employed in these studies. Variation in the inhibition of plasmin and chymotrypsin with disease has not received so much attention.

There have been no previous reports of changes in an accurately measurable biological phenomenon occurring consistently with changes in proteolytic inhibition. Therefore it has been difficult to relate changes in proteolytic inhibition to other biological phenomena. In the work to be presented, normal and pathological variations in proteolytic inhibition were analyzed. The relationship between proteolytic inhibition and other biological measurements was studied in an attempt to gain information concerning the significance of changes in proteolytic inhibition.

Materials and Methods

Patients.—Observations on patients with neoplastic diseases were made on the medical and surgical services at Memorial Hospital and James Ewing Hospital. Patients with various other diseases were studied by permission of the Department of Medicine at New York Hospital and by permission of the Columbia Medical Division at Bellevue Hospital. Measurements of proteolytic inhibition were done on blood samples taken on the day of admission to the hospital, prior to the start of treatment. However, a number of patients with lymphoma or leukemia had received x-ray therapy in the course of their illness prior to admis-

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sion to the hospital, and most of the patients with tuberculosis had received some form of treatment.

Serum proteolytic inhibition of 65 normal individuals and of 117 patients was measured as described in Paper II and the determinations are shown in Figs. 1 to 3 of Paper II. Other measurements of serum proteolytic inhibition in the present paper were also done by the method described in Paper II.

Sedimentation rate was determined by the method of Wintrobe and Landsberg (4).

Plasma fibrinogen was separated as fibrin by the clotting method of Cullen and Van Slyke (5), and nitrogen determination was done by the micro-Kjeldahl method. The determination on each sample was done in duplicate and averaged.

Typhoid vaccine was a preparation obtained from Lederle Laboratories called typhoid-paratyphoid vaccine for non-specific protein therapy. 1 cc. contained 100×10^6 killed bacteria.

RESULTS

Variation in Proteolytic Inhibition in Normal Individuals

The variation in inhibition of plasmin, trypsin, and chymotrypsin in 65 normal adult individuals was shown in Figs. 1 to 3 of Paper II. For plasmin the 2 sigma variation was 44 per cent of the mean, for trypsin it was 64 per cent, and for chymotrypsin it was 34 per cent. This observed variation in normal sera was not due to experimental error alone, since the variation found when a single normal serum was run 15 times (*i.e.*, experimental error) was much less than the variation found among different normal sera. With plasmin the 2 sigma variation was 20 per cent of the mean and with trypsin it was 28 per cent.

Approximately two-thirds of the subjects in the group of 65 normal individuals were male and one-third were female; approximately two-thirds were fasting, and one-third had eaten within 4 hours of the determination. For each enzyme, there was no difference in the mean value of inhibition between males and females or between fasting and non-fasting subjects. The variations of inhibition within the normal range did not appear to be related to sex or the recentness of food ingestion.

When inhibition of plasmin and trypsin was determined for one male individual at frequent intervals over a period of several months, the variation in inhibition was no greater than that for repeated determinations on a single serum sample. The serum inhibition of plasmin and trypsin was constant for any one individual over a long period of time.

Correlation of Clinical Data with Abnormal Proteolytic Inhibition

It was shown in Paper II that a large percentage of patients with cancer, various acute diseases, and tuberculosis had increased inhibition for trypsin and chymotrypsin, while few had increased inhibition for plasmin. Trypsin inhibition was different from plasmin inhibition, but could not be distinguished from chymotrypsin inhibition. Whatever is said about trypsin inhibition, therefore, also applies to chymotrypsin inhibition.

1. Clinical Data and Plasmin Inhibition.—There were too few instances of increased plasmin inhibition (Fig. 1, Paper II) to permit any correlation to be made with clinical data. It was interesting to note that the patient with the highest level of plasmin inhibition maintained the same level on repeated determinations during a 1 year period. The condition for which he had been admitted (tuberculosis) gradually improved during the period of observation.

TABLE I

Inhibition of Trypsin by Sera of Patients with Neoplastic Diseases

The 3 patients with Hodgkin's disease, the 2 patients with chronic lymphatic leukemia, and the 2 patients with lymphosarcoma that showed increased inhibition had received x-ray therapy prior to admission. The level of inhibition of all other cases was determined before any treatment was given.

Type of neoplastic disease	No. of subjects observed	No. showing normal inhibition	No. showing increased inhibition
Cancer of the large bowel and rectum	7	2	5
Cancer of the stomach	5	1	4
Cancer of the tongue	4	0	4
Cancer of the esophagus	2	1	1
Hodgkin's disease	5	2	3
Chronic lymphatic leukemia	3	1	2
Lymphosarcoma	3	1	2
Multiple myeloma	2	1	1
Chronic myeloid leukemia	1	1	0
Acute lymphatic leukemia	1	1	0
Cancer of the breast	10	9	1
Cancer of the prostate	5	2	3
Cancer of the lung	5	0	5
Cancer of the cervix	5	2	3
Abdominal carcinomatosis	3	0	3
Cancer of the bladder	2	1	1
Cancer of the liver	2	1	1
Basal cell carcinoma	2	2	0
Fibrosarcoma	1	0	1
Seminoma	1	0	1
Totals	69	28	41

2. Clinical Data and Trypsin Inhibition.—Of the patients with neoplastic disease (Fig. 2, Paper II), 55 per cent showed increased trypsin inhibition. In Table I are listed the types of neoplastic diseases studied and the number of each type which showed normal or increased trypsin inhibition. By correlating the level of trypsin inhibition with the histological appearance of the various tumors (obtained by biopsy, operative removal, or autopsy) it appeared that increased trypsin inhibition was associated chiefly with processes that

brought about cellular destruction. The presence of increased trypsin inhibition and the degree of increase were more closely related to the amount of disintegration and inflammatory reaction in the tumor than to other factors such as type, size, or duration of the tumor. Those tumors most prone to ulceration and secondary infection showed a high correlation with increased trypsin inhibition (*e.g.*, cancer of the lung, tongue, stomach, large bowel, and rectum), while cancer of the breast, although metastic in 8 of the 10 patients studied, did not.

In the patients with lymphoma or leukemia, increased trypsin inhibition was more closely related to the recentness of x-ray radiation that the patients

TABLE II

Inhibition of Trypsin by Sera of Patients with Acute Diseases

The level of inhibition was determined on the day of admission. The 2 patients with lobar pneumonia that showed normal inhibition and the 2 patients with myocardial infarction that showed normal inhibition had had symptoms for less than 2 days. All other patients had had symptoms for more than 2 days.

Disease process	No. of subjects observed	No. showing normal inhibition	No. showing increased inhibition
Lobar pneumonia	9	2	7
Primary atypical (virus) pneumonia	3	3	0
Coronary occlusion	3	2	1
Acute rheumatic fever	3	0	3
Osteomyelitis	2	0	2
Bronchiectasis	2	0	2
Virus hepatitis	2	1	1
Infectious mononucleosis	2	1	1
Cellulitis of the hand	1	0	1
Lung abscess	1	0	1
Totals	28	9	19

had received than to the extent of the disease. Patients with incipient or advanced lymphomatous or leukemic conditions had normal trypsin inhibition if no x-ray treatment had been given beforehand, while patients who had received x-ray treatment within 2 weeks of the measurement had elevated trypsin inhibition regardless of the stage of the disease.

The types of *acute diseases* studied and the number of each type showing normal or increased trypsin inhibition are listed in Table II. All the patients studied were admitted to the hospital after symptoms had been present for 2 days or more, with the exception of 2 patients with pneumonia and 2 patients with myocardial infarction. 68 per cent of the patients had increased inhibition. The degree of increase was greatest with acute bacterial infection, particularly if the disease was well established at the time of measurement.

The 2 patients with lobar pneumonia who were seen when symptoms had been present for less than 2 days were found to have normal trypsin inhibition, in contrast to other patients with lobar pneumonia who were seen later in the course of the disease. The changes in trypsin inhibition were followed in these 2 early cases of pneumonia, in another case of lobar pneumonia of 3 days' duration, and in 2 cases of myocardial infarction of recent occurrence. In the patients with pneumonia (Table III), trypsin inhibition rose rapidly during the first few days in spite of effective penicillin treatment, reached a peak at approximately the 4th to the 6th day of illness, and then gradually declined to normal in the subsequent week or two. In the period of decline, trypsin inhibition was still significantly elevated while the patient showed no signs or symptoms of disease. In the cases of myocardial infarction (Table IV), trypsin inhibition remained normal for at least 5 days after onset of the illness, rose gradually to a peak near the 10th day of illness, then gradually declined to normal. Thus, inhibition could be normal in the early stages of an acute process and elevated when other manifestations of the disease had cleared. Similar observations were made by Jobling *et al.* (6) in a study of the changes in trypsin inhibition during the course of pneumonia.

TABLE III

Inhibition of Trypsin by Sera of Patients with Lobar Pneumonia During the Course of the Disease

Description in text. Inhibition expressed as micrograms of trypsin inhibited by 4.2×10^{-4} ml. of serum. All patients were treated with penicillin.

Duration of illness	Trypsin inhibited		
	Case 1	Case 2	Case 3
days	γ	γ	γ
1	1.25	—	—
2	1.20	1.30	—
3	1.57	2.04	1.98
4	2.30	2.53	2.50
5	—	—	3.00
6	1.98	2.83	—
7	—	—	2.70
10	1.50	2.00	2.00
14	1.17	1.40	1.86
17	—	1.32	1.47

In patients with acute diseases the development of increased trypsin inhibition appeared to be related to tissue destruction. Inhibition was higher when tissue involvement was more extensive. An uncomplicated process of tissue necrosis such as myocardial infarction was associated with significant and prolonged increases in trypsin inhibition. The stage of the disease at which trypsin inhibition increased also suggested that cellular destruction preceded the development of increased inhibition. This was especially noticeable in

cases of myocardial infarction, in which the elapsed time before increased inhibition developed was about the time usually required for gross tissue degeneration to become evident.

A large percentage of the *patients with tuberculosis* (Fig. 2, Paper II) showed increased trypsin inhibition, but it was impossible to associate the extent of a tuberculous process with the amount of inhibition. Although all the cases studied were considered to have active tuberculosis, diagnostic limitations prevented a critical appraisal of the activity of the disease in each case. In this small series there was no correlation between the level of trypsin inhibition and such objective criteria of activity as the amount of cavitation or the value of the Gaffky count.

TABLE IV

Inhibition of Trypsin by Sera of Patients with Myocardial Infarction Compared to the Sedimentation Rate during the Course of the Disease

Inhibition expressed as micrograms of trypsin inhibited by 4.2×10^{-4} ml. of serum. Sedimentation rate corrected for hematocrit value.

Duration of illness	Case 1		Case 2	
	Trypsin inhibited	Sedimentation rate	Trypsin inhibited	Sedimentation rate
days	γ	*mm./hr.*	γ	*mm./hr.*
1	1.25	8	—	—
3	—	—	0.74	10
5	1.00	12	0.85	6
7	1.90	30	2.00	30
10	3.20	55	2.78	45
14	3.01	42	2.53	48
21	1.92	28	2.04	32
28	1.30	12	1.04	13

Correlation of Laboratory Findings with Abnormal Proteolytic Inhibition

1. Laboratory Data and Plasmin Inhibition.—The few instances of increased plasmin inhibition did not permit any correlation to be made with laboratory data.

2. Laboratory Data and Trypsin Inhibition.—All types of cases were analyzed together in an attempt to demonstrate a possible relationship between increased trypsin inhibition and abnormalities in some usual laboratory measurement.

There was no consistent relationship between normal and abnormal trypsin inhibition and normal or abnormal plasma proteins, blood urea nitrogen, alkaline phosphatase, liver function tests, or electrolyte balance. As has been shown previously (6, 7), there was also no consistent relationship between changes in trypsin inhibition and changes in the white count or temperature.

A direct relationship was found, however, between one simple laboratory procedure and increased trypsin inhibition. 100 per cent of the cases showing a significantly elevated sedimentation rate had increased trypsin inhibition, and none of the cases with a normal sedimentation rate had increased trypsin inhibition. The correlation was based on sedimentation rate determinations done in 31 of the 117 cases studied, excluding the patients with myocardial infarction. The relationship between trypsin inhibition and the sedimentation rate was particularly striking in the cases of myocardial infarction (Table IV).

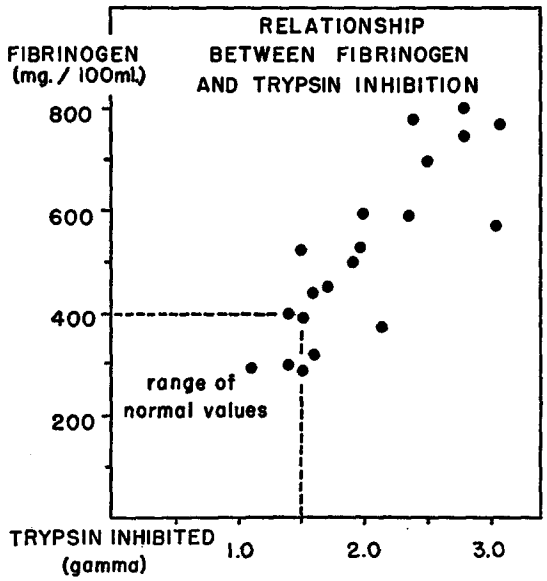

FIG. 1. Comparison of the level of inhibition of trypsin with the fibrinogen concentration in 20 blood samples. Description in text. Inhibition of trypsin expressed as micrograms inhibited by 4.2×10^{-4} ml. of serum. Fibrinogen expressed as mg. per 100 ml.

3. Fibrinogen Concentration and Trypsin Inhibition.—Since elevation of the sedimentation rate has been shown to be dependent primarily upon elevation of fibrinogen concentration (8), 20 additional patients were studied to compare the level of trypsin inhibition with the fibrinogen concentration. The 20 patients had undergone extensive surgery for various neoplastic diseases; all were 5 to 7 days postoperative and had had febrile courses. Results of the comparison are shown in Fig. 1. There was close correlation between fibrinogen concentration and the level of trypsin inhibition. In every instance in which fibrinogen concentration was increased, trypsin inhibition was also increased (within experimental error), and *vice versa*. Moreover, the increases in both trypsin inhibition and fibrinogen concentration were quantitatively similar.

Correlation between Experimentally Produced Increases in Trypsin Inhibition and Fibrinogen Concentration

Ham and Curtis (9) found that intravenous injections of typhoid vaccine would produce prolonged elevation of the fibrinogen level in human beings. In view of the close correlation between fibrinogen concentration and the level of trypsin inhibition demonstrated above, the effects of intravenous typhoid vaccine on serum proteolytic inhibition and fibrinogen concentration were compared.

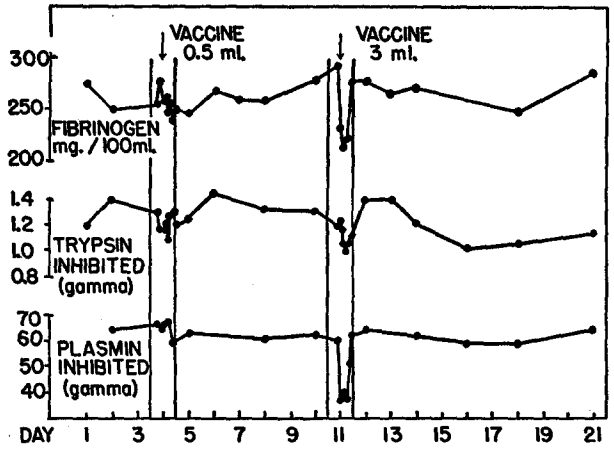

FIG. 2. The effect of intravenous typhoid vaccine on fibrinogen concentration and the level of inhibition of trypsin and plasmin. Subject, J. M., 43 year old male. Description in text. Each cc. of typhoid vaccine contained 100×10^6 killed bacilli. Time of injection indicated by arrow. Inhibition of trypsin expressed as micrograms inhibited by 4.2×10^{-4} ml. of serum. Inhibition of plasmin expressed as micrograms inhibited by 1.65×10^{-3} ml. of serum. Fibrinogen expressed as mg. per 100 ml.

The subjects used were patients on the Medical Service of the James Ewing Hospital. The first subject, J. M., was a morphine addict, taking ¼ grain of morphine every 4 hours; he was admitted on pretext and no medical abnormality was found. The other 3 subjects each had had a meningioma removed 6 months or more prior to admission; they were receiving physical therapy for paralytic contractures. All subjects were otherwise healthy, normal adults.

Preliminary measurements were made on each subject prior to injecting typhoid vaccine. After the injection, blood samples were taken every 45 to 90 minutes in the first 5 hours (the immediate postinjection period). In the next 8 hours, 2 or 3 more samples were taken, and after that, 1 sample was taken every 1 to 3 days for the remaining period of observation. Plasma and serum samples were immediately frozen and stored at −15°C. Each procedure was carried out on all samples from one experiment at the same time. Frozen samples were thawed just prior to their use.

The effects of intravenous typhoid vaccine on fibrinogen concentration and the level of trypsin and plasmin inhibition are shown in Figs. 2 to 6. Of chief

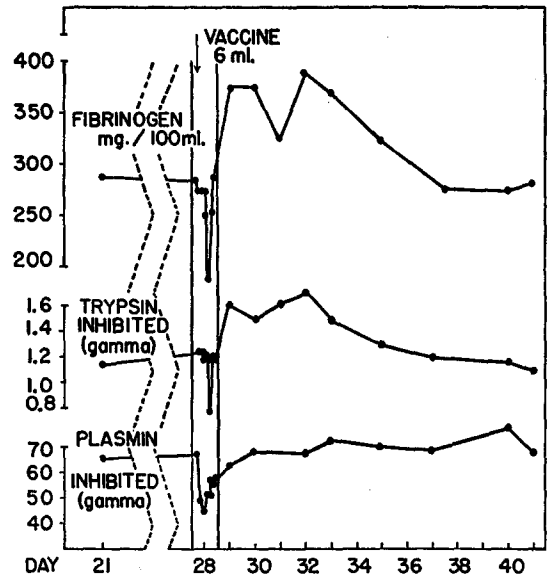

FIG. 3. The effect of intravenous typhoid vaccine on fibrinogen concentration and the level of inhibition of trypsin and plasmin. Continuation of observations on J. M., 43 year old male, from the 21st day. Conditions as in Fig. 2.

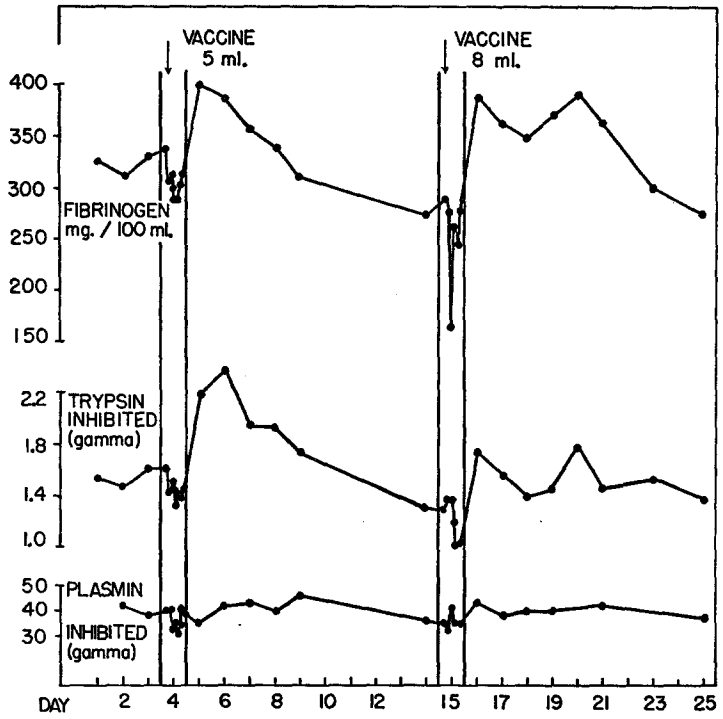

FIG. 4. The effect of intravenous typhoid vaccine on fibrinogen concentration and the level of inhibition of trypsin and plasmin. Subject, L. N., 45 year old male. Conditions as in Fig. 2.

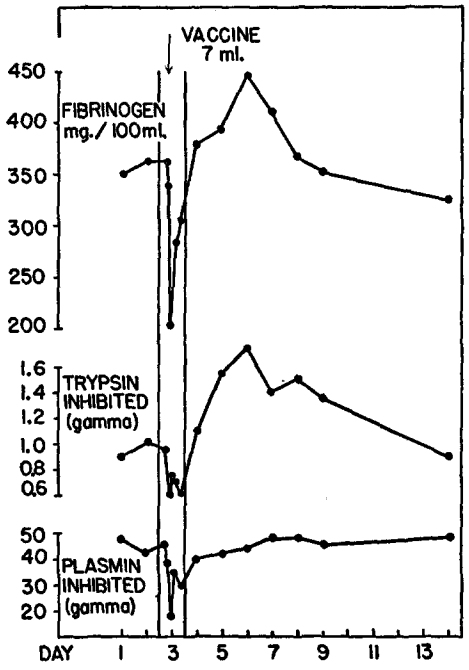

FIG. 5. The effect of intravenous typhoid vaccine on fibrinogen concentration and the level of inhibition of trypsin and plasmin. Subject, R. C., 48 year old female. Conditions as in Fig. 2.

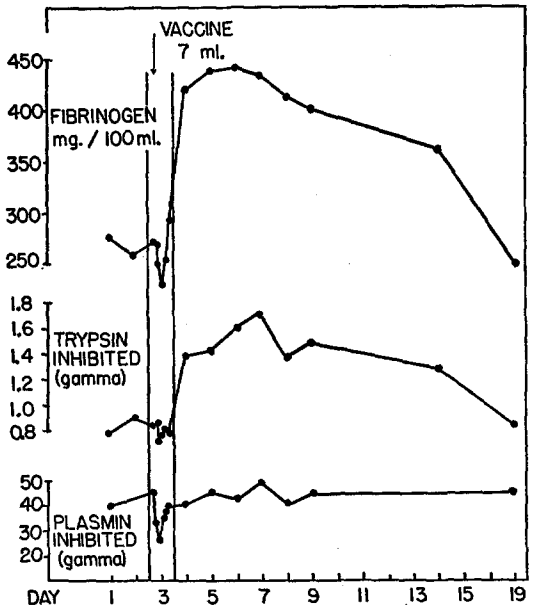

FIG. 6. The effect of intravenous typhoid vaccine on fibrinogen concentration and the level of inhibition of trypsin and plasmin. Subject, L. G., 40 year old female. Conditions as in Fig. 2.

interest at present are the changes in the measurements that occurred beginning 1 day after the vaccine injection. When small amounts of vaccine were used (Fig. 2), there was no significant alteration in any of the measurements in the period beginning 1 day after injection. With the larger amounts of vaccine (Figs. 3 to 6), an increase in fibrinogen concentration above the baseline value was evident 1 day later. The maximum value of fibrinogen concentration was reached within 24 to 72 hours after injection. The subsequent decrease to the baseline level was more gradual, requiring 6 to 12 days. Changes in trypsin inhibition (beginning 1 day after injection) were parallel with those of the fibrinogen concentration. Both the temporal and the quantitative aspects of the changes in these two measurements were alike. Serum proteolytic inhibition was specifically elevated for trypsin, since at no time did the inhibition for plasmin rise above normal.

In the *immediate* postinjection period there was an inconstant decrease in fibrinogen as well as in inhibition of trypsin and plasmin. Whenever such a decrease in these measurements occurred, an active proteolytic enzyme was present in the blood samples taken shortly after the injection. This phenomenon and other phenomena occurring in the immediate postinjection period are being investigated at present to determine their possible relationship to the subsequent development of increased trypsin inhibition and fibrinogen concentration.

DISCUSSION

Previous workers demonstrated that trypsin inhibition by serum is increased in a variety of diseases; *e.g.*, in acute bacterial infections such as pneumonia (1) and typhoid fever (7), in chronic diseases such as tuberculosis, rheumatic fever, and nephritis (7, 11), in hyperthyroidism (7), and in all forms of neoplastic diseases (10, 11). It was pointed out by several early investigators (7, 12, 13) that a factor which the various disease states have in common is tissue destruction of some type, and they therefore suggested that tissue destruction plays a role in the development of increased trypsin inhibition. More recently Raab (14) came to the same conclusion after finding that the increase of trypsin inhibition in patients with cancer was related chiefly to the presence of tissue disintegration in the tumor.

In the present study a clinical analysis was made of the relationship of the level of trypsin inhibition to the stage of the disease process, to histological changes in tissues, and to some special instances of tissue destruction (myocardial infarction and x-radiation) as well as to the various types of diseases. This analysis provided additional evidence that the development of increased trypsin inhibition is related to tissue destruction.

The clinical evidence for the relationship between increased trypsin inhibition and tissue destruction is supported by the finding that increased trypsin inhibition is associated with an increase in the fibrinogen concentration (or sedimentation rate). It has been shown by numerous studies (reviewed by Ham and Curtis (9)) that the fibrinogen concentration (or sedimentation

rate) is increased by processes of tissue destruction, whether bacterial, neoplastic, traumatic, or chemical in origin.

A close relationship was found between elevated trypsin inhibition and increased sedimentation rate. In the cases of myocardial infarction that were studied, changes in these two measurements paralleled each other throughout the course of the disease. In 20 patients, increases in the level of trypsin inhibition and the fibrinogen concentration were found to be quantitatively alike. By the injection of typhoid vaccine, it was found that not only were increases in trypsin inhibition and fibrinogen quantitatively alike, but also the time of changes in the two measurements was the same. These several findings substantiate each other.

Data that have been obtained concerning the circumstances associated with variations in trypsin inhibition have never been compared with data obtained concerning the variation in fibrinogen concentration (or sedimentation rate). A comparison of these two separate sets of data bears out the experimental observations above that trypsin inhibition and fibrinogen level vary together. In this comparison the review of the literature by Ham and Curtis (9) is used as the chief source of information on the variation in fibrinogen level.

The *normal variation* in trypsin inhibition and fibrinogen concentration is similar. In the group of normal individuals studied, the variation in trypsin inhibition is 64 per cent of the mean and the variation in fibrinogen concentration is reported to be 50 per cent of the mean (9). It was found that, in a single individual during health, trypsin inhibition shows a 28 per cent variation from the mean and the fibrinogen concentration is reported to show an 18 per cent variation in one individual over a comparable period of time (9). Variation in the two measurements in a group of individuals and in a single individual are even more alike than these values would indicate, for the experimental error in determining trypsin inhibition was somewhat greater than the error in determining fibrinogen. For both measurements the range of variation in a series of normal subjects is greater than the variation in any one subject during health.

In the present work it was found that trypsin inhibition is not affected by recent food ingestion. This finding is in agreement with the study by Jobling *et al.* (15) on the effect of food ingestion on trypsin inhibition in dogs. The fibrinogen concentration also is not influenced by recent food ingestion (9). It was found by Rosenthal (16) that long periods of starvation decreased the level of trypsin inhibition in rabbits and it is known that the level of fibrinogen in human beings is decreased in association with nutritional deficiency (9).

The *pathological variation* in trypsin inhibition and fibrinogen concentration is similar. All the disease states which have been shown to be associated with increased trypsin inhibition are also associated with elevation of the fibrinogen concentration (or sedimentation rate). It has been shown that trypsin inhibition could be normal in the early stages of an acute process and elevated when

other manifestations of the disease had cleared. Changes in fibrinogen concentration in disease occur in a similar way (9). It was also shown above by simultaneous determination of the two measurements (Figs. 3 to 6) that changes in each are parallel following an injection of typhoid vaccine. The increase in trypsin inhibition in the various diseases rarely exceeds 3 times the normal value, and increases in fibrinogen concentration in disease are of the same order of magnitude.

Trypsin inhibition was found, in the present study as well as in previous studies (6, 7), to vary independently of temperature, white count, plasma protein concentration, and other chemical determinations on the blood. Fibrinogen concentration likewise varies independently of these various measurements (9).

Pregnancy is the only "normal" physiological condition associated with increased fibrinogen concentration. Similarly pregnancy is the only normal circumstance in which trypsin inhibition is increased. When data on changes in trypsin inhibition during pregnancy (17) are compared with the data on changes in fibrinogen concentration during pregnancy (18), it is seen that increases in trypsin inhibition occur at the same stage of pregnancy and persist for the same length of time after parturition as do increases in fibrinogen concentration.

Diagnostically, an abnormal elevation of trypsin inhibition has the same significance as an elevated fibrinogen concentration. It therefore has the same significance as an elevation of the sedimentation rate if increased sedimentation is due to changes in fibrinogen concentration and not to other factors such as abnormal plasma globulins, lipemia, or changes in erythrocyte size. In the absence of pregnancy, elevated trypsin inhibition affords laboratory evidence for an organic disease process which may be present at the time of observation or which may have terminated several days or weeks before. As in the case of a slight rise in fibrinogen, a slight increase in trypsin inhibition above the individual's norm may not result in a level of trypsin inhibition beyond statistically normal limits. Such a moderate response in trypsin inhibition would not be detected without previous knowledge of the level during health, but nevertheless may represent a trypsin inhibition response of pathological significance for the individual. Elevation of trypsin inhibition is a non-specific indication of disease and tissue destruction; there is no apparent value in using the measurement of trypsin inhibition as a specific diagnostic test.

The factors associated with changes in plasmin inhibition and the physiological significance of increased plasmin inhibition are as yet unknown.

The question of why trypsin inhibition and fibrinogen concentration vary together remains to be answered. Certainly fibrinogen itself does not inhibit trypsin. It is known that plasma and serum inhibit trypsin to the same extent, and in Paper I it was shown that tryptic digestion of fibrinogen was increased by increasing the concentration of the fibrinogen substrate. In the typhoid vaccine experiments there was no indication as to whether one measurement

changed before the other. With the available data, no definite conclusions can be drawn as to whether an increase in one substance is the cause of an increase in the other substance or whether increases in both are fortuitously related. Further work is indicated to determine the significance of the association between changes in fibrinogen concentration and trypsin inhibition.

SUMMARY

Variation in the inhibition of trypsin, chymotrypsin, and plasmin by serum was studied in 65 normal individuals and in 117 patients with a variety of diseases.

It was shown that elevated inhibition for trypsin and chymotrypsin is associated with disease processes that bring about cellular destruction.

Changes in the inhibition of trypsin and chymotrypsin were closely correlated with changes in the erythrocyte sedimentation rate and fibrinogen concentration that occur in association with disease.

Intravenous typhoid vaccine was found to produce parallel changes in the inhibition of trypsin and chymotrypsin and in the fibrinogen concentration in human beings.

It was concluded that the diagnostic significance of increased trypsin or chymotrypsin inhibition is the same as that of increased fibrinogen concentration; it is a common, non-specific response to a variety of pathological conditions and has no value as a specific diagnostic test.

Increased plasmin inhibition occurred too infrequently to permit detailed study.

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