Chronic Antithrombinaemia (Antithrombin V) with Haemorrhagic Diathesis in a Case of Rheumatoid Arthritis with Hypergammaglobulinaemia*)

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Introduction

During the last 5 years our clinic has made a follow-up study on a case which in many respects has offered considerable difficulties. The patient shows clinical features of slowly progressive rheumatoid arthritis, associated with gradually aggravating hypergammaglobulinaemia and with disorders in the coagulative mechanism resulting in haemorrhagic tendencies.

Since neither the clinical picture itself nor the anomaly demonstrated has been mentioned in the literature as a cause of marked decrease in blood coagulability it seems justified to present a detailed report on the clinical findings and the data on the pathology of coagulation in this case, the more so because this acquired haemorrhagic diathesis was successfully treated.

Case History

A dutch man of unmixed race, aged 45, initially workman in a coal industry and subsequently employed as a driver, has been known to us since 1942. His symptoms date back to 1937—1938, and have given rise to partial invalidity in 1942, followed by complete invalidity in 1948.

Symptomatology. The symptoms which predominated in the inital period (1937—1951) were those of varying degress of not very painful swelling and gradually aggravating functional impairment of the larger *joints* (knee, shoulder, elbow and ankle joints). Functional impairment markedly aggravated after 1947. It was not until autumn 1955, that the complete picture of rheumatoid arthritis developed, with painful swelling also of the smaller joints (proximal digital joints of upper and lower extremities, wrist, jaw and foot joints (Fig. 1, 2).

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*) A preliminary report of this case, which will be published in Ned. T'schr. v. Geneesk. (74), has been given on the occasion of the Congres of Dutch Society of Haematology at Utrecht (November, 24th, 1956).
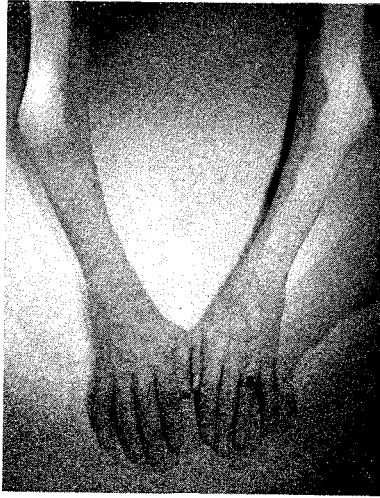
F i g . 1 :   Photograph of the arms in January, 1956: old (elbow) and fresh articular changes (proximal
digital and wrist joints) of rheumatoid arthritis.

F i g . 2 :   Photograph of the distal part of the legs in January, 1956: scars of the haemorrhages of
1951—1952. Arthritic changes in the knee and foot joints.

Both rheumatological and radiological findings seemed to justify the dia
gnosis rheumatoid polyarthritis. Only the radiological features of elbow and

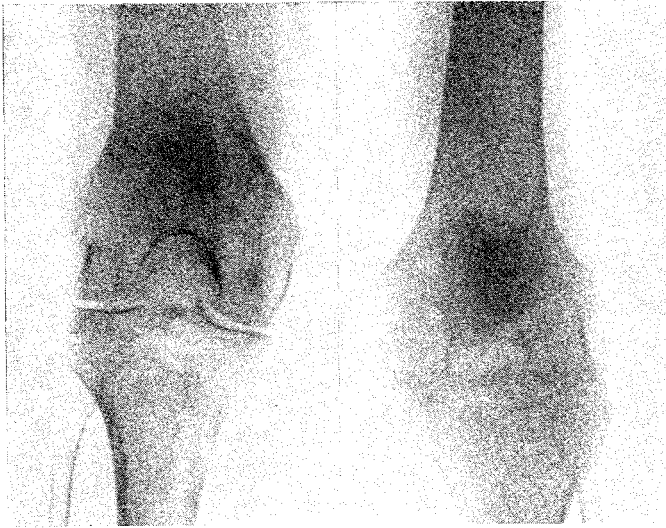knee-joints (bilateral) were highly reminiscent of the X-ray changes seen in cases of haemophilia (Fig. 3).

F i g . 3 : x-ray of the knee-joints in January, 1956, before cortisone treatment was given).

At no time were rheumatic nodules found. A diagnostic biopsy from one of the joint capsules was rejected by the patient. Puncture of a knee-joint in 1942 yielded an exudate which was rich in leucocytes and bacteriologically sterile. Repeated punctures made since 1942 have been without results.

In addition to the intra-articular changes involving functional impairment there occurred symptoms of a *haemorrhagic diathesis*, viz: in 1951 the patient showed a spontaneously "cutaneous apoplexy" of the distal part of the right leg and the left thigh. (Fig. 4).
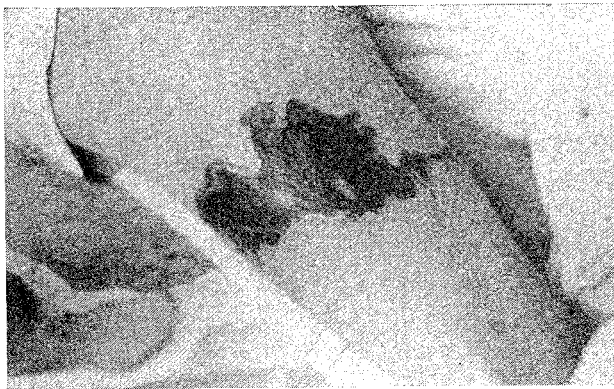

F i g . 4 / 5 : Fresh and slightly older "cutaneous apoplexy" (cutaneous haemorrhage) of the distal parts of the legs in 1952.

A few days later, these cutaneous changes — exulcerated haematoma — were reminiscent of tropical ulcer. With the exception of the first day they were painless and they showed no unusual inflammatory manifestations. Transient painful swelling of the left upper arm must be interpreted as a muscular haematoma. Apart from these localizations there was a haematoma of the wall of the bladder with painful micturition and haematuria, and a haematoma of the right gluteus maximus. The faeces showed a positive benzidine reaction. At no time could haemorrhages in the joints be demonstrated with certainty. As a result of another haemorrhage in the right distal leg, localized around the old lesion, and a cutaneous haemorrhage in the distal part of the left leg, the patient was re-admitted in 1952. A few weeks later in the course of this hospitalization there was another acute and initially very painful haemorrhage of the distal part of the right leg, in and around the already granulating wound. On the day after the haemorrhage there was a large black spot with vesiculation both in and outside the existing granulations (Fig. 5).
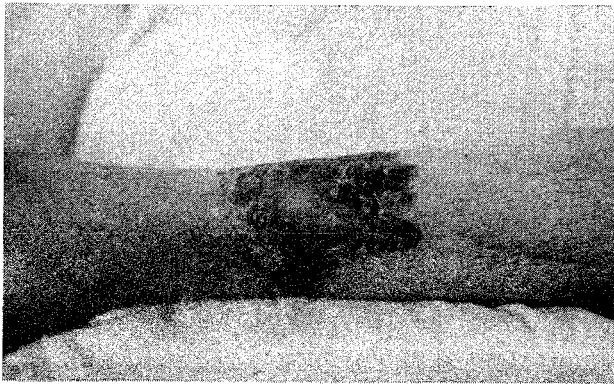

Fig. 5

A few months later a haematoma of the right pectoral muscle led to treatment with ACTH: the ulcers healed completely if very slowly (see description of clinical course). During the period 1952—1955 there was only microhaematuria and sometimes loss of occult blood in the stools. In 1956, at the site of a von Pirquet reaction, marked haemorrhagic inbibition of the skin developed, without necrosis. The recurrent „cutaneous apoplexies" were very suggestive of a vascular affection. The ocular fundus was normal and neurological examination, supplemented by EEG, remained negative. The numerous ECG's were suggestive of a normal coronary circulation. We were unable to perform a capillary microscopic examination. A cutaneous muscle-fascia biopsy showed no anomalies in the vascular wall or in the intermediate substance. *Polymicro-adenopathy* was the third remarkable feature encountered

in this case. In the autumn months of 1955 there was painless swelling of the lymph glands, which felt rather firm but showed no adhesion either to the skin or to each other. Localizations were the cervical region, the supraclavicular, axillary, bicipital and inguinal regions. The spleen seemed to be only just palpable; percussion suggested slight enlargement.

The remaining organs never showed any pathology. Heart and lungs were normal. The blood pressure was invariably about 120/80. There were no gastrointestinal anomalies. Renal function was normal, and repeated intravenous pyelography failed to reveal any anomalies. The skin showed favourable trophic characteristics and was blemished only by the scars of „cutaneous apoplexies" surrounded by some pigmentation. There were no findings which tended to indicate an endocrinological affection.

It seemed to us to be very important that the patient never had a fever, never felt dysphoria and never was excessively tired or apathic. The patient's weight remained virtually constant throughout all these years.

Laboratory findings (not including data of coagulation analysis):

The ESR (determined according to W e s t e r g r e n) was 45/73 mm. during the first and the second hour in 1942. Values found in subsequent years were, except during treatment, invariably above 100 mm (1st and 2nd h., fig. 14). The ESR in defibrinized blood, too, was always markedly increased up to the same values.

The peripheral blood picture invariably showed a normal leucocyte count with normal subdivision. The red blood picture was that of mild hypochromic anaemia (8—10.5 g./100 ml. haemoglobin concentration) with a moderately increased reticulocyte count. There was as a rule a slight increase in thrombocytes. The sternal bone marrow showed very active erythropoiesis and thrombopoiesis; leucopoiesis was not remarkable. There was unmistakable hyperplasia of the reticular and the plasma-cellular elements (101). Needle biopsy of the axillary lymph glands (in 1956) showed hyperplasia of the lymphatic and the reticular cells. No signs indicating malignancy were found either in the bone marrow or in the glandular punctate.

Immunohaematological examination revealed no iso-antibodies or auto-antibodies against erythrocytes. There was a normal urinary and faecal excretion of urobilinogen. It was impossible, due to the patient's lack of co-operation, to determine the erythrocyte survival time. Serum iron values and the results of the H i j m a n s v a n d e n B e r g h reaction (always negative, directly and indirectly) were always low (total bilirubin fluctuated about 0.35 mg./ 100 ml.). There was otherwise marked pseudo agglutination of erythrocytes, which often precluded an erythrocyte count. Varyingly positive results of reactions to antibodies against leucocytes and thrombocytes were attributed to repeated blood transfusions. At no time could the lupus erythematosus cell phenomenon be demonstrated (Z i m m e r - H a r g r a v e s method [138]).

Blood serology: the reactions according to M e i n i c k e, K a h n and W a s s e r m a n n were invariably negative, as was the agglutination reaction to brucella Bang. The antistreptolysin titre was not above 1 : 250 (threshold value). The anti-I titre was 0, and the anti-0 titre 1 : 40 positive. The R o s e test yielded no result beyond normal limits (max. 1 : 8).

Bacteriology: the v o n P i r q u e t reaction was invariably markedly positive. The cultures of gastric contents, urine and intra-articular fluid always remained negative for tubercle bacilli.

The urine contained but a trace of protein and varying quantities of erythrocytes, with sometimes some leucocytes. The bacteriology was invariably negative.

As to liver function tests it can be stated that all were entirely normal, with the exception of protein turbidity tests, which were highly pathological as a result of dysproteinaemia (H a e n g e r after 24 hours 4 +; ZnSO₄ once 36.8; thymol turbidity test 8—12 U.). Normal

test findings: cholesterol 180 mg/100 ml., with 50—75% esterification; bromsulphalein excretion within 30 minutes more than 95%; galactose tolerance testing showed an excretion of 3.5 g. in the first sample of urine. Alkaline phosphatase, too, was normal with values of about 5 U. (K i n g - A r m s t r o n g).

There was never an increase of Congo red retention.

Chemical determination of the protein pattern showed a fibrinogen content in the plasma of 1.5 g./100 ml. The total protein values throughout the years showed an increase from 10 g./100 ml. to 12 g./100 ml. There was unmistakable reversal of the protein pattern, viz: albumin 2 g./100 ml. and even less, globulins to a maximum of 10 g./100 ml (without fibrinogen). Quantitative paper electrophoresis*) (58, 87) showed a marked increase in γ-globulins to a value slightly above 8 g./100 ml. (Fig. 6); the gamma peak had a broad base.

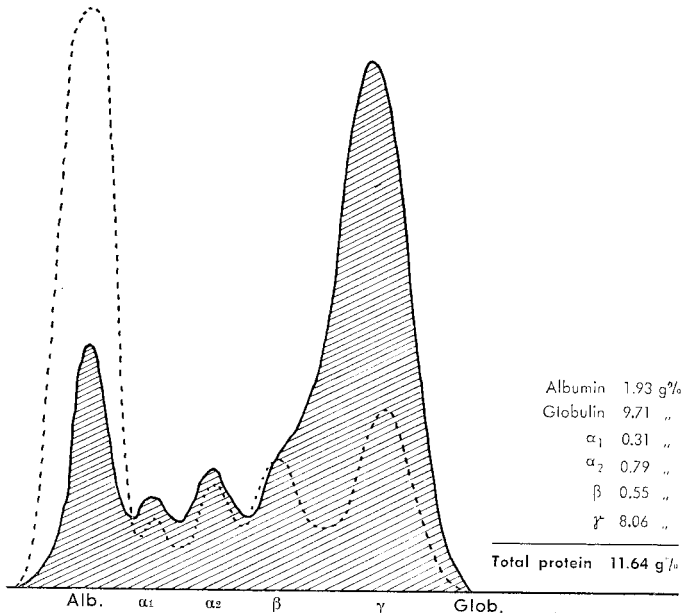| Albumin | 1.93 g% |
Globulin	9.71 „
α_1	0.31 „
α_2	0.79 „
β	0.55 „
γ	8.06 „
Total protein	11.64 g/.

F i g . 6 : Quantitative serum paper electrophoresis before cortisone treatment (December, 1955).

No pathological proteins were demonstrable. The euglobulin test (S i a) was negative. Repeated tests for cryoglobulins and pyroglobulins were also negative.

Ultracentrifugation*) of undiluted and diluted serum (the 1 : 5 dilution proved the most suitable) showed a marked increase in the "normal" γ-globulin value (S 7); the albumin value (S 4) was very low. The β-globulin value was slightly above the normal. There was no increase in macroglobulins.

Investigation into the Anomalies of the Blood Clotting Mechanism**)

The coagulation time of blood (obtained by skin punction), determined at room temperature and using ordinary glassware, has shown an increase since

*) We thank Dr. J. A. v a n d e r V e k e n of the Institute for Flowerbulb Research, Lisse, and Dr. H. K. O o s t e r h u i s of the „Laboratorium voor chemische physiologie", Amsterdam, for having carried out these investigations for us.

**) This investigation could be realized only with the support of the firm F. Hoffmann-La Roche, Basle, Switzerland.

the patient's first admission in 1951 (15—60 minutes, at control values of 5—8 minutes).

The *bleeding time* as determined by the D u k e method was always within the normal limits of 1—3 minutes. The R u m p e l - L e e d e phenomenon was invariably negative. The *recalcification time* according to H o w e l l was 150—170 seconds. The *heparin tolerance* determined by thrombin titration according to Q u i c k , showed an increase (Fig. 7).
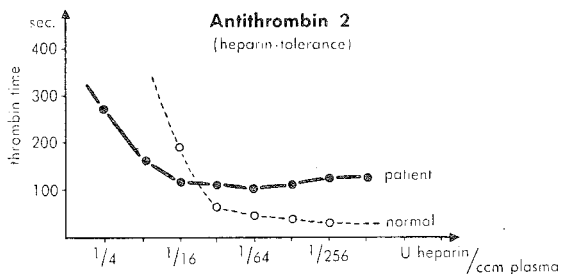

F i g . 7 : Demonstration of the increase in heparin tolerance of the patient's plasma: by addition of various quantities of heparin to normal thrombocyte-poor oxalate plasma the thrombin time is increased with increasing heparin concentrations (dotted line). Quantities of heparin which, added to normal plasma, cause immeasurably long thrombin times, still yielded measurable times in the patient's thrombocyte-poor oxalate plasma (bold black line); in other words the patient's plasma develops a subnormal antithrombin-II activity following addition of heparin.

The heparin tolerance time according to M a r b e t and W i n t e r s t e i n (79) corresponded with the slightly increased recalcification time (150—180 seconds). Determination of the heparin tolerance time by recalcification with a calcium solution containing 10 γ heparin/ccm, however, yielded a value slightly below the normal (8 minutes as against the normal 10); in this experiment, too, therefore, an increase in heparin tolerance was observed. Blood clot *retraction*, measured at 37⁰ C., showed normal velocity and intensity. The *thrombocyte* count, determined by the H e r w e r d e n (47) method, varied from 300,000 to 500,000 (normally 200,000—300,000). The thromboplastin-producing and the heparin-neutralizing properties of the thrombocytes (factors 3 and 4) were separately determined; both were normal. The B i g g s and M c f a r l a n e method (10) was used in determining the intensity of *intrinsic thromboplastin production;* there was no difference from normal controls. The residual pro-thrombin 3 hours after coagulation was less than 0.5%/o (normal *prothrombin consumption).* On the basis of these findings the conclusion was formed that the activity of the *antihaemophilic* factors VIII and IX as well as the PTA, H a g e m a n - and S t u a r t factor must be sufficient (20, 46, 49, 51, 95, 97). The findings also seemed to exclude any excess in circulating *antithromboplasti-nogen* or in *antithromboplastin.* Nor was there an excess in *antiprothrombin,* as *thrombin formation* (10) showed practically normal intensity (Fig. 8).
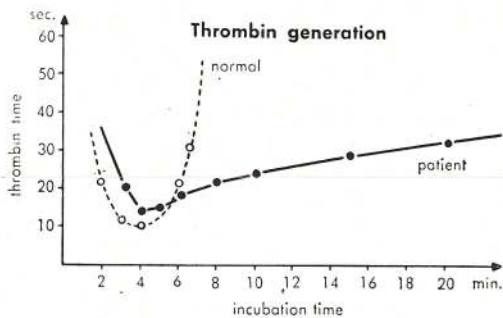
F i g . 8 : Thrombin generation test: the rate of thrombin formation in the patient's plasma was measured according to the M a c f a r l a n e and B i g g s principle (10); the maximum of thrombin activity is unmistakably slightly lower and is reached slightly later than normal. Again a striking feature is the decreased intensity of metathrombin formation, which is expressed in the flat rise in the bold black line.

The *fibrinogen* level, determined by the desalination method (13), with values of 1—1,5 g./100 ml., showed a marked increase. No increase in *fibrinolytic* activity was seen (4).

The *prothrombin activity*, determined by Q u i c k ' s original method, using acetone-dried human cerebral thromboplastin (93), showed a considerable decrease to values of 20—30% (i. e. a "prothrombin" time of 22,5—32 seconds, at a 12 second control). In view of this prolongation of the "prothrombin" time the quantity of factor II *(prothrombin)* and the activity of factor V *(pro-accelerin)*, factor VII *(proconvertin)* and factor X (Stuart) were submitted to quantitative determination (73). Factors II, VII and X were always sufficiently active (60—100%). The activity of factor V, however, with values of 30—60%, proved to be slightly decreased; in no case, however, could this be used to explain prolongation of the "prothrombin" time. Only determination of the *thrombin time* (4, 94) furnished the key to the solution of the problem of the prolonged clotting time and "prothrombin" time: 0.2 ml. platelet poor oxalate plasma did not clot until 50—70 seconds after addition of 0,1 ml. thrombin solution *(Topostasin "Roche"*, 10 U./ml. distilled water), as against the 10—12 seconds for normal plasma.

In this way an excess of *antithrombin or antifibrinogen* was thus demonstrated. In order to determine the nature of the anticoagulant the various antithrombins (I—IV according to S e e g e r s ' classification [110]) and the possible other antithrombin or antifibrinogen properties of the plasma and the serum were investigated (129), viz:

a) *antithrombin-I* (i. e. fibrinogen):
As has been pointed out, the fibrinogen level showed an unmistakable increase. Determination of the thrombin time in increasingly diluted plasma (with a M i c h a e l i s buffer pH 7.42) likewise revealed high fibrinogen values. The activity curve of the thrombin-fibrinogen-fibrin reaction was proportionate,

from plasma dilution 1 : 16, to that in control plasma with the same increase in fibrinogen (Fig. 9).
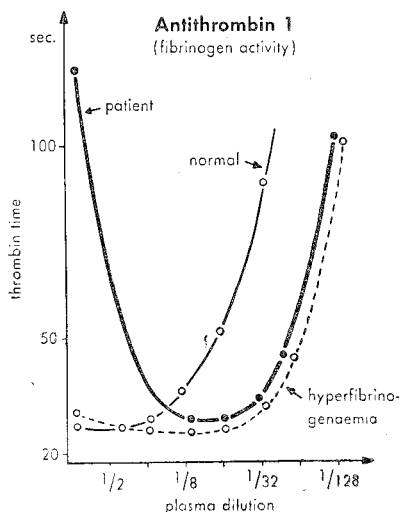
F i g . 9 : The thrombin times of oxalate plasma and its dilutions (with M i c h a e l i s buffer at pH 7.42) were determined by the thrombin titration method according to Q u i c k : a) in normal plasma (thin black line), b) in patient's plasma (bold black line) and c) in plasma from a patient showing only an increase in fibrinogen corresponding in intensity with the increase in fibrinogen in our case (dotted line). The thrombin concentration was about 2 I. U./ml. distilled water. From a dilution of 1 : 16 there is a virtual parallelism between the line representing our patient's value and that representing the value in the case with an increase in fibrinogen only, i.e. in the higher dilutions the thrombin time is a measure of the rapidity of reaction between thrombin and fibrinogen or, in other words, it is a measure of the fibrinogen level (relative excess of thrombin!). In the dilutions below 1 : 16 the antithrombin-V activity is more markedly manifested to the extend to which the dilution decreases.

The increase in fibrinogen does not explain the prolongation in clotting, thrombin and „prothrombin“ time which was found; a similarly marked increase in fibrinogen is fairly often seen without any considerable clotting anomaly associated (96).

b) *antithrombin-II* (i.e. heparin + heparin co-factor) (31, 37, 50, 51, 52, 56, 118):

A circulating anticoagulant of this type was excluded on the basis of the following three experiments:

— *in vitro:* various concentrations of protamine sulphate had no significant effect on the thrombin time;

— *in vivo:* intravenous injection of various quantities of protamine sulphate caused no reduction of the markedly prolonged clotting time;

— *thrombelastography:* hyperheparinaemia yields a picture entirely different than that seen in this case (45, 84). Viz. Fig. 17.

The increased heparin tolerance (see front) is probably attributable to a decrease in the activity of the heparin co-factor.

c) *antithrombin-III* (i.e. antithrombin progressive or metathrombinogen), (15, 36, 38, 40, 41, 53, 54, 64, 65, 71, 88):

This antithrombin, which transforms active thrombin into inactive meta-thrombin, and which can be held responsible for the fact that, within a short time after the completion of the normal clotting process, nearly all thrombin activity has disappeared from the serum, seemed to be decreased in our case, if only because the serum still contained a striking quantity of demonstrable free thrombin (about 12 U./ml.) three hours after coagulation. A corroboration was found in the result of the thrombin generation test; the thrombin formed in this test proved to disappear at an extremely slow rate (Fig. 8). Quantitative determination of the activity of antithrombin-III confirmed these two findings; it was found to be less than 25% of normal antithrombin-III activity (Fig. 10).
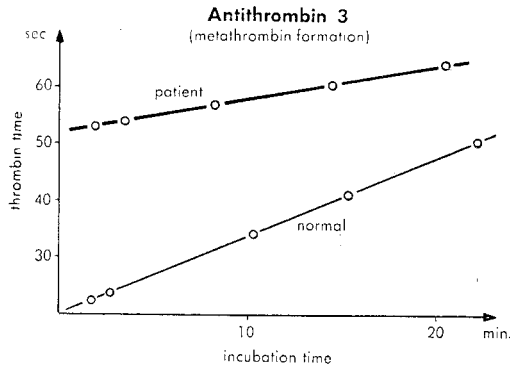

F i g . 1 0 : Demonstration of the antithrombin-3 activity: about 3 I.U. thrombin/ml. was added to a dilution of the patient's serum and of normal serum (1 : 10 with a M i c h a e l i s buffer at pH 7.42) at 23° C. The metathrombin formation in the patient's serum shows considerable retardation (bold, slightly elevated rising line). The higher initial value in the patient's serum is based on the activity of antithrom-bin-5! As substrate for the measurement of thrombin-time we used a solution of bovine fibrinogen (150 mg/ 100 ml. NaCl 0,9%).

d) *antithrombin-IV:* According to S e e g e r s this antithrombin appears in the course of the clotting process, subsequently to disappear again (92). It is no longer demonstrable in the serum. Its action is based on marked activation of antithrombin-III in the course of coagulation. No method of determining this antithrombin has been developed as yet. Neither an increase nor a decrease in this antithrombin, however, would explain the coagulation disorder seen in this case.

e) *antithrombin-V* (not described as such by S e e g e r s) : We apply this term to a plasma factor with an antithrombin function which, like anti-thrombin-II, immediately inactivates thrombin („antithrombine immédiate") but, unlike antithrombin-II, has no direct effect on thromboplastin and thrombin formation. Our subsequent experiments were based on the hypothesis that

(physiological?) antithrombin-V showed a marked increase in our patient. The following properties of antithrombin-V were investigated:

1. *Coagulophysiological properties:*

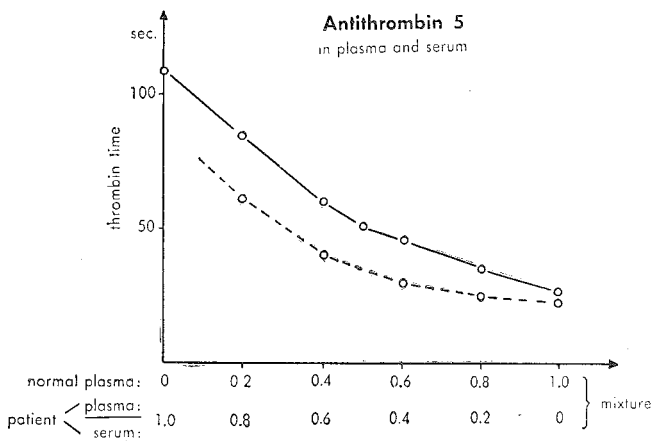An increase in antithrombin-V was demonstrable both in the plasma and in the serum (Fig. 11).

F i g . 1 1 : Determination of the antithrombin-V content (activity) in the patient's plasma and serum with the aid of determination of the thrombin time. The serum also shows an unmistakable antithrombin-V activity, but slightly less marked than that in the plasma (probably due to the lower fibrinogen content and partial saturation of the antithrombin-V during the process of coagulation).

The increase found prior to treatment amounted to about ten times the normal activity of antithrombin-V (Fig. 12).
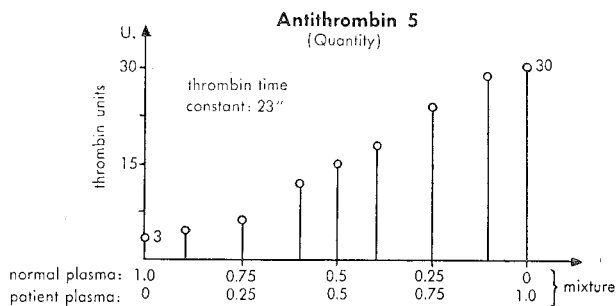
F i g . 1 2 : Determination of the activity of antithrombin-V : 0,1 ml of thrombin solution (3 I. U. thrombin/ml distilled water) added to 0.1 ml normal plasma, gives a thrombin time of 23″. The same time is obtained with the patient's plasma if a tenfold quantity of thrombin (30 I. U./ml distilled water) is added to it.

This increase to ten times the normal value can also be disclosed by determination of the plasma thrombin time and its dilutions up to 1 : 128, as

compared with plasma showing only an increase in fibrinogen (Fig. 9). The increase in antithrombin-V is also manifested by the values of antithrombin-III activity; the initial value in the patient's serum in this determination is considerably higher than that in normal controls (Fig. 10).

Antithrombin-V is a *thrombin inhibitor;* it does not destroy thrombin. A certain quantity of thrombin which is added to the patient's serum is largely inactivated by the markedly increased antithrombin-V, but it regains its full activity as the serum is diluted (measured on the basis of the rate of fibrinogen-fibrin conversion [Fig. 13]). These findings, too, exclude the possibility of a deficiency in fibrinogen accelerator as a cause of the prolonged thrombin time (99).
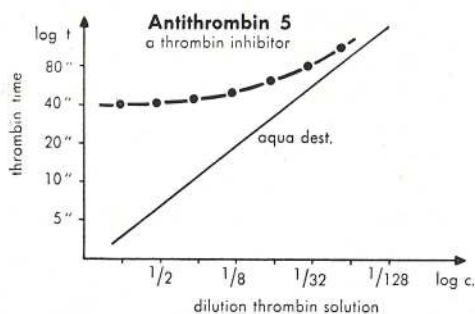

Fig. 13: Demonstration of the correlation between the thrombin time (measured by the rate of conversion of a fibrinogen solution of 150 mg/100 ml) and the thrombin concentration at which a) a thrombin solution of 20 I. U./ml distilled water, and b) a thrombin solution of 20 I. U./ml patient serum is diluted in distilled water (bold line). The thrombin solutions were kept at a temperature of 4° C. To the extent to which the serum (antithrombin-V) is diluted the thrombin times approach the straight line of the dilution curve of thrombin in distilled water, i. e. the antithrombin effect diminishes; the same result was obtained using dilutions with physiological saline solution.

The properties of antithrombin-V are recognized in the globulin fraction. There are indications suggesting that they are dependent on the *γ-globulins.* The patient's serum was dialysed against distilled water (pH 6.5) for 2×24 hours at 4° C. In the course of this process a protein precipitate was formed which was submitted to electrophoretic analysis; it proved to have a high concentration of γ-globulins (> 75%). Following this dialysis the serum showed almost complete disappearance or at least a marked decrease of the thrombin inhibitor property. The precipitated protein, however, which was re-dissolved by dialysis against a physiological NaCl solution, showed anti-thrombin-V activity comparable to that seen in untreated serum.

We were also able to demonstrate, in a number of preliminary experiments, that the same dialytic fraction of normal serum — if concentrated — shows a very intensive similar thrombininhibiting function; electrophoresis showed that this precipitate from normal serum likewise consisted chiefly of γ-globulins.

Antithrombin-V is *no antifibrinogen.* If a certain quantity of thrombin, dissolved in distilled water, is added to a series of fibrinogen solutions of

decreasing concentration, then the coagulation time of this fibrinogen solution is increased to the extent to which the dilution is increased. The same experiment was made with the patient's serum replacing the distilled water (the thrombin added to the serum is converted into metathrombin only to a very slight degree, as the patient's antithrombin-III has an extremely low activity, especially if the serum is kept at 4° C.); clotting times read at a fibrinogen concentration of about 1 : 10 (30 mg./100 ml.) were in the order of the values found in the serial dilution with distilled water. In the presence of an antifibrinogen the times obtained with the highly diluted fibrinogen would have become immeasurably long.

The nature of clot formation itself, moreover, as seen in the patient's blood, gives no indications suggestive of an abnormal conversion of fibrinogen into fibrin such as is frequently seen in multiple myeloma and in macroglobulin-aemia (6, 72); we refer to the normal aspect of clot formation shown in the thrombelastogram.

2. *Physicochemical properties:*

The patient's antithrombin-V behaves as a protein inasmuch as it can be destroyed by heating to 100° C. for 10 minutes (10 minutes' heating to 56° C. had no demonstrable effect on the activity of antithrombin-V). Antithrombin-V is not dialysable and is not adsorbed onto $BaSO_4$. The anticoagulant seems not to be extractable with ether. It behaves as a euglobulin, i.e. it is not soluble in distilled water. Electrophoretically the activity of antithrombin-V lies probably within the γ-fraction, of which it is only a very small component (less than 2%) that binds the antithrombin.

Further investigations are to be made in this field.

3. *Serological and radiological properties:*

Suitable methods to be used in this type of protein investigation are still in the early stage of development at our clinic, and were therefore not used in this case.

Clinical Course during Treatment with ACTH and Cortisone

In view of the fact that the activity of "antithrombine immédiate" decreases during treatment with ACTH (66), this hormonal therapy was instituted in our case as early as 1952 (6 $\times$ 7 I. U. daily, from April 20th to June 1st). The

haemorrhagic ulcerations soon healed. Systematic investigation of the clotting mechanism was not yet feasible in those days. In view of the decrease in the ESR (Fig. 14), however, it would seem to us that an improvement in the disordered clotting mechanism must have occurred at the time, analogous to that seen in 1956 during treatment with Cortisone (Fig. 14). Although ACTH treatment was stopped there was no recurrence of cutaneous or muscular haemorrhages. There was, however, a marked increase in the microscopic loss of blood

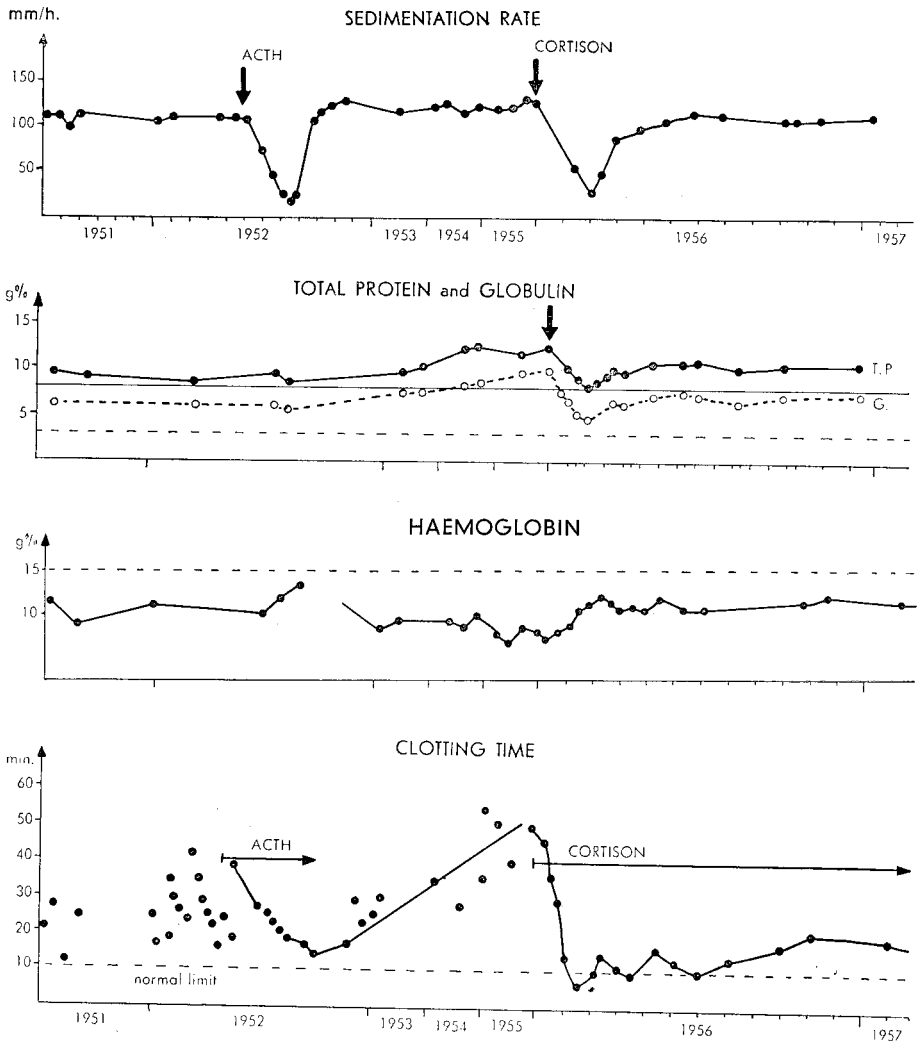F i g . 1 4 : Course of ESR, total protein and serum globulin values, haemoglobin content and coagulation times during the period 1951—1957. A decrease in globulins from 10 to 5 g/100 ml (gammaglobulins from 8 to 3 g/100 ml) is associated with an increase in albumin value from 1.9 to 3.2 g/100 ml and a decrease in clotting time to values approaching the normal (1956—1957).

in the urine, and sometimes also in the faeces, especially during 1955. Increasing hypochromic anaemia developed, and the disturbances in the protein pattern showed slowly progressive aggravation, parallel with which the clotting time gradually increased (Fig. 14).

The patient never had any complaints, not even as to tiredness. At no time were cutaneous or mucosal petechiae seen. In view of the slightness of symptoms treatment remained symptomatic throughout the period 1952—1955 (a few fresh blood transfusions, and oral ferro-therapy).

Towards the end of 1955 rheumatoid arthritis recurred, with swelling and tenderness of the small digital joints and of the jaw, elbow, wrist and foot joints (Fig. 1 and 2). There was also polymicro-adenopathy (lymph glands the size of a pea or hazelnut, not tender to touch, fairly firm on palpation and detached from each other as well as from adjacent parts), and mild swelling of the spleen (palpation dubious). The patient was not febrile at any time.

This recurrence led to re-admission, after which the findings described in the first part of this paper were obtained. The imminent haemorrhage, the favourable clinical experience with ACTH in 1952 and the subsequent reports on cortisone and blood coagulation (62) formed a reason to institute prolonged cortisone treatment. Remarkable improvement was seen in the course of this therapy, viz: disappearance of the polyarthritis and the polymicro-adenopathy, a decrease in the γ-globulin level from 8 to 3 g./100 ml. and a parallel decrease in the activity of antithrombin-V (Fig. 15, 16) with normalization of the clotting time (Fig. 17); the "prothrombin" time, too, showed a decrease from 32 to 16 seconds (normally 12 seconds).

Electrophoresis

before treatment   during treatment

1 m.   8 m.

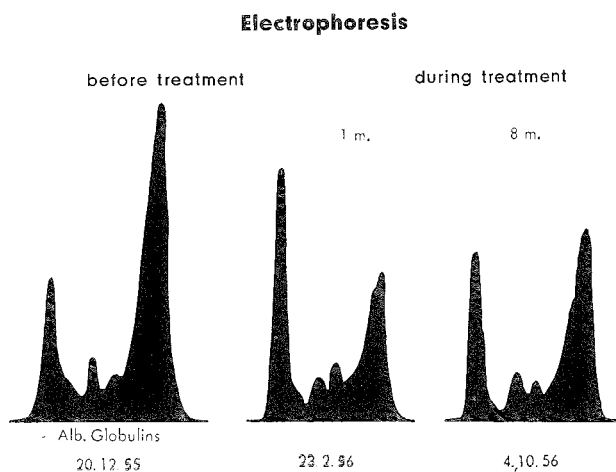- Alb. Globulins

20.12.55   23.2.56   4.10.56

F i g . 1 5 : Quantitative paper electrophoresis before and during treatment: a month after institution of cortisone treatment there is considerable improvement. Seven months later there is some slight exacerbation.

Further improvements included a marked decrease in microscopic loss of blood and a rapid increase in the haemoglobin level. The function of the knee joints was improved by physiotherapy.
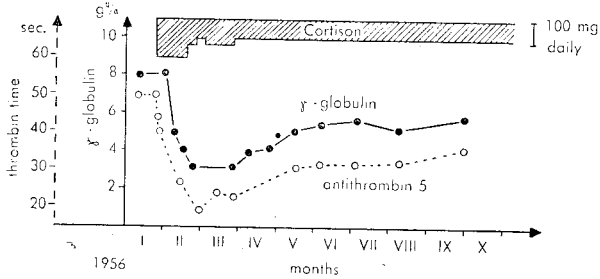
F i g . 1 6 : Gamma-globulin and antithrombin-V values during cortisone treatment. Striking parallelism in the decrease. Our latest value (April 14th, 1957) hardly differs from the last value included in the graphic (October 4th, 1956). The therapeutic improvement, therefore, has reached a stationary level. Normal thrombin times in these experiments 10—12 sec.
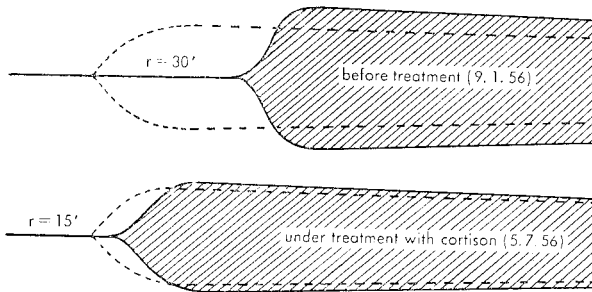
F i g . 1 7 : Thrombelastogram of untreated venous blood before and after cortisone treatment, compared with the normal thrombelastogram (dotted line). Striking improvement during treatment.

Administration of cortisone (3 × 25 mg daily) has been continued over a year. The γ-globulin values after an initial very marked decrease, have slowly increased again but are still considerably below the pretherapeutic level. The wrist and foot joints, too, have unmistakably swollen again, but without any pain. The lymph glands also are slightly swollen again. The blood coagulation time and the antithrombin-V activity are slightly increased again, in accordance with the increase in γ-globulin value (Fig. 14, 16). This regression, however, has not hitherto been such as to necessitate a change in treatment. The patient has no complaints.

Discussion

The discussion will be divided into two parts, viz: one concerning clinical diagnosis and one concerning changes in the mechanism of coagulation.

Clinical diagnosis and differential diagnosis

The rheumatologist's[*]) diagnosis that the patient is suffering from rheumatoid arthritis is based on the history, the clinical picture and the radiological aspects of the joints (103a). We would have liked to have found rheumatic nodules and positive serological reactions in support of this diagnosis.

Rheumatoid arthritis is sometimes associated with a rather marked increase in γ-globulins and in fibrinogen (90, 103, 105). Cases of rheumatoid arthritis with a serum γ-globulin value of more than 8 g/100 ml, however, have not hitherto been described in the literature available to us. Another unusual feature in the course of this case of rheumatoid arthritis is the occurrence of polymicro-adenopathy and of haemorrhagic tendencies. In our opinion both symptoms should be considered correlated with the extremely marked hypergammaglobulinaemia, not only because this preceded the onset of the two symptoms, but also because the glandular punctate revealed (reactive?) hyperplasia of the lymphoreticular apparatus while, on the other hand, a very active anticoagulant was found in the globulin fraction of the serum protein pattern rich of γ-globulins. During treatment with cortison, moreover, both the swelling of the lymph glands and the marked increase in anticoagulant concentration disappeared to an extent proportionate to the degree of decrease in γ-globulin value.

The cutaneous manifestations of the haemorrhagic tendencies are also unusual: haemorrhages were not limited to the subcutis but spread into the cutis itself, which subsequently became necrotic. A similar picture is known in dermatology as "apoplexie cutanée" which is encountered chiefly in cases of periarteritis nodosa (polyarteritis), during anticoagulant therapy with the aid of coumarol derivatives (hypersensitivity angiitis [59, 123, 137]) and also perhaps in cases with a possible mechanism of the type of the Shwartzman-Sanarelli phenomenon (117). But no clinical or pathological anatomical findings were obtained to confirm this suggestion.

The radiological changes in the elbow and knee joints were immediately suggestive of chronic haemarthrotic changes of the type characteristic of haemophilia. It is undoubtedly possible, if not probable, that recurrent haemorrhages occurred in the knee joints of this patient, which are the site of least resistance due to the changes caused by the arthritic process, as a result of static weight bearing.

The clinical features of the haemorrhagic diathesis are by no means typical neither of haemophilia and haemophilia like diseases nor of thrombopathia and capillaropathia (102, 114). Never we have found a prolonged bleeding time or a positive Rumpel-Leede phenomenon. The syndrome of hyperglobulinaemic purpura Waldenström (43, 82, 108, 125, 126, 127, 128), which has become a classical syndrome although its aetiology is still obscure, and which is sometimes associated with the symptoms of rheumatoid arthritis, can be excluded if only in view of the fact that the type of purpura described by Waldenström was at no time seen in this patient, and also because the history includes nothing to suggest the extreme tiredness which is a typical symptom of this affection. Macroglobulinaemia (6, 42, 55, 63, 77, 78, 83, 107, 125), which was also described by Waldenström and which is also associated with haemorrhagic tendencies, but as a rule with extremely characteristic mucosal, retinal and micromacular cutaneous haemorrhages, need not be taken into account, not only because this type of haemorrhage was lacking in this case, but particularly because an increase in the macroglobulin fraction was excluded with certainty. Both syndromes or clinical entities described by Waldenström, moreover, are characterized by rather typical changes in the bone marrow, which we were unable to demonstrate in this case (mutatis mutandis this also holds true for multiple myeloma, which is associated particularly with mucosal haemorrhages and cutaneous petechiae (76, 126). Repeated attempts failed to provoke the phagocytosis

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*) We are indepted to Dr. H. Colenbrander from the Department of Rheumatology, University Hospital, Leyden, for his consultative advices.

phenomenon characterizing *lupus erythematosus*, which may show either symptomatic macro-globulinaemia or a severe disturbance in coagulation as a cause of haemorrhagic diathesis (70, 98).

The diseases mentioned invariably entail hypergammaglobulinaemia. Such an increase of γ-globulins is also described as symptomatic macroglobulinaemia in *congenital syphilis* (130). In view of the negative findings in our case, however, both congenital and acquired syphilis would seem to be excluded. Other chronic bacterial infections, e.g. *subacute bacterial endo-carditis*, chronic *tuberculosis* and also *bronchiectases*, may be associated with marked hypergammaglobulinaemia. Our patient showed no sign suggestive of any of these disorders. Nor were there any signs suggestive of chronic inflammatory processes such as *kala azar, inguinal granuloma* and *sarcoidosis*, which have been described as associated with extreme hypergammaglobulinaemia (19, 106, 121). A marked increase in γ-globulins is also seen in *chronic hepatitis* (or cirrhosis of the liver); the patient's liver feels supple on palpation and liver function tests are normal.

The last possibility taken into account was that of malignant tumour. The history, covering a period of more than 20 years, and the excellent clinical condition still prevalent, render "malignancy" improbable. The cytological findings in the sternal punctate and the protein pattern constitute a complete argument against the possibility of K a h l e r ' s disease (18, 126, 135). The patient's serum contained no demonstrable cryoglobulins or pyroglobulins (81, 100, 104, 136). The cytological picture of the reticular, lymphatic and plasmacellular elements of the bone marrow and the lymph glands was that of (reactive) hyperplasia. Characteristics of malignancy were lacking (14). On the basis of cytological criteria, too, aleukaemic *leukaemia* can be excluded with certainty, as also any other *malignant affection of the reticulo-endothelial system* (e.g. histiosarcoma or H o d g k i n ' s sarcoma, etc.).

On the basis of these considerations regarding differential diagnosis *no other conclusion* can be reached than that this patient is suffering from rheumatoid arthritis with hypergammaglobulinaemia, associated with polymicro-adenopathy and haemorrhagic tendencies. Pathogenically the hypergammaglobulinaemia should be regarded as an expression of extreme hyperergia of the lymphoreticular apparatus, which according to W a l d e n s t r ö m is a phenomenon of *hyperimmunization.* The aetiology in this case remains obscure.

Disorders in the mechanism of coagulation

The pathology of the blood clotting mechanism in this patient was manifested in the *triad: increased clotting-, thrombin- and "prothrombin" time.*

The history alone suffices to indicate the improbability of *congenital* haemorrhagic tendencies. The haemophilic states (haemophilia A and B, PTA, S t u a r t and H a g e m a n factor deficiency), moreover, as a rule show an increase in clotting time only. Only seldom do these cases of congenital haemorrhagic diathesis also show an increase in prothrombin time due to factor V, VII or S t u a r t factor deficiency. An increased thrombin time is not encountered in any of the abovementioned affections. The same holds true for parahaemophilia and thrombopathia haemophilica (23). Only in cases of congenital (or acquired) *hypofibrinogenaemia* can the triad described be encountered. In this case, however, there was nothing to suggest fibrinogen deficiency.

Among the *acquired* disorders of coagulation caused by *circulating para-proteins,* W a l d e n s t r ö m's macroglobulinaemia may show a slight increase in clotting time (6, 72, 120) and multiple myeloma even the lack of any firm clot formation (32, 76). It is presumed that the protective colloid effect of pathological proteins inhibits the conversion of fibrinogen into fibrin (polymerization); this presupposes an *antifibrinogen.* No anticoagulant acting as an anti-fibrinogen was demonstrable in our patient's blood.

Another possibility to be taken into account is an excess in *circulating anti-thromboplastic anticoagulant* ("Hemmkörperhaemophilie" according to D e u t s c h) (7, 17, 21, 22, 26, 27, 34, 35, 44, 50, 75, 91, 111, 124), particularly since this has also been described as found in hypergammaglobulinaemia (85) and in rheumatic disease (48). The increased clotting time in those cases, however, is a result of directly inhibited thromboplastin formation; "prothrombin" time and thrombin time in cases with inhibited thromboplastin formation show no significant increase; only in case of a circulating-anticoagulant in systemic L. E. the "prothrombin" time may be markedly prolonged, because this anticoagulant is not only an antithromboplastin, but also an antiprothrombin (34, 70, 98). The blood in our case contained no anticoagulant neither with a thromboplastin formation inhibiting nor with a directly antithromboplastic, or antiprothrombic effect.

Heparinaemia, i.e. an increase in *circulating antithrombin-II,* also shows the abovementioned triad (5, 11, 12). Apart from an antithrombic effect, however, heparin also has a marked antithromboplastic effect; not only is thromboplastin formation retarded but it is also diminished, which is manifested by a pathological prothrombin consumption among other things (80). Besides iatrogenic heparinaemia there is the acute endogenous heparinaemia seen in anaphylactic and other shock conditions (28, 29, 31, 57, 92). K o l l e r , G a s s e r , K r u e s i and M u r a l t described two cases of purpura fulminans with factor V deficiency, in one of which they found a circulating anticoagulant which could be neutralized with the aid of protamine sulphate (68, 69). The more subacute form of endogenous heparinaemia is seen following whole-body irradiation, sometimes in cases of leukaemia etc. (2, 112). Cases of chronic idiopathic (congenital?) heparinaemia have also been described in which the anticoagulant, however, was but inadequately characterized as heparin (8, 9, 24, 115). In normal serum G r e e n s p a n detected a mucoprotein metachromatically stainable with toluidin blue and with heparinoid properties which could be neutralized with protamine sulphate (39). N i l s s o n and W e n c k e r t recently succeeded in isolating, from normal human blood, an anticoagulant which corresponded with heparin as to its antithrombic and antithromboplastic function *(heparin-like antithrombin* [86]). No increase in antithrombin-II was seen in our patient; the heparin tolerance was found to be even higher than normal.

We believe that the cause of the increase in clotting, "prothrombin" and thrombin time in our patient should be found in a marked increase in the concentration of a *purely antithrombic circulating anticoagulant,* not identical with heparin and referred to, in accordance with S e e g e r s' nomenclature, as *antithrombin-V* (bearing in mind that this is not necessarily a new antithrombin but merely one which has not hitherto been described in detail by S e e g e r s). As to blood coagulation antithrombin-V has a few properties which correspond with those of heparin-antithrombin, viz: both have an immediate effect ("antithrombine immédiate") and manifest themselves in an increased clotting, "prothrombin" and thrombin time. Unlike heparin, however, antithrombin-V exerts no influence on the intensity of thromboplastin and thrombin formation. Patients suffering from heparinaemia show haemophilization (33, 84), i.e. there is pathological thromboplastin and thrombin formation, associated with a markedly delayed increase in elasticity of the blood clot and insufficient prothrombin consumption during and after coagulation. This haemophilization was not found in our patient. Also unlike heparin, antithrombin-V cannot be neutralized with the aid of protamine sulphate. The difference between blood clotting in the case of an excess of antithrombin-II and that in the case of an excess of antithrombin-V is clearly demonstrable by thrombelastography: whereas heparinaemia is associated not only with increased reaction time but also with a delayed increase in clot elasticity (84), an excess of antithrombin-V (see Fig. 17) combines an increased reaction time with a virtually normal elasticity curve.

Partly on the basis of the thrombelastographic findings (normal course of clot formation) we believe ourselves to be justified in suggesting the following hypothesis as to the blood coagulation process in our patient:

All coagulative factors required for slow thrombin formation are available and show virtually normal quantities and activities in our patient's blood. The thrombin liberated during slow thrombin formation, however, is immediately inactivated by the highly active antithrombin-V (inhibition). This means that the active form of factor V, which is indispensable in rapid thrombin formation, cannot be produced in time; the thrombin slowly formed in the early phase of blood coagulation, it should be borne in mind, is responsible for the activation of factor V and therefore indirectly for rapid thrombin formation. Consequently the beginning of clot formation is postponed (increased clotting time).

Since the formation of intrinsic thromboplastin in our patient's blood took place with normal intensity, thrombin formation should also show normal intensity as soon as the inhibition (antithrombin-V) has been overcome. This is indeed the case, as shown by the thrombin generation test (retarded onset but normal intensity). Fibrin formation following the rapid phase of thrombin formation is normal (normal thrombelastographic findings). The maximal elasticity of the clot even exceeded that in normal blood clots, probably as a result

of the slight increase in the thrombocyte count, the increase of fibrinogen and the severe increase of the sedimentation rate. Clot retraction follows in time and shows normal intensity. Fibrinolysis shows no increase. The extent to which the markedly decreased activity of antithrombin-III is involved in the clotting process remains yet to be established with certainty. Normal antithrombin-3 activity would probably cause an even more marked increase in the clotting time in this case because the thrombin inhibited by antithrombin-V would then be neutralized at an increasing rate of speed (i.e. conversed into metathrombin), as a result of which no quantity of thrombin sufficient to activate factor V would ever become available.

We have been unable to find an observation in the literature which makes mention of a patient with chronic haemorrhagic tendencies showing a markedly increased blood clotting time caused by a marked increase in concentration of an anticoagulant with the properties of antithrombin-V, and showing an un-mistakable parallelism between the intensity of disorders of coagulation and that of the hypergammaglobulinaemia. In a case of true haemophilia described by S o u l i e r treatment with thrombin was followed by the occurrence of a species-specific antithrombin; this antithrombin, however, was not directed against the patient's own thrombin, as was seen in our case (113). J u e r g e n s pointed out that, particularly in affections associated with stimulation of the reticulo-endothelial system ("Immunitätsvorgänge"), a heparin-like antithrom-bin is found which, in the degree of its activity, shows some parallelism with the γ-globulin values determined (60, 61, 62); no increased clotting time was demonstrable in these cases. Investigations covered cases of acute and recurrent hepatitis, various forms of cirrhosis of the liver, bronchial asthma, chronic bronchitis, etc. W i t t e and D i r n b e r g e r use the term "heparin-antithrom-bin" or "thrombin inhibitor" (131, 132, 133), thereby apparently referring to the same anticoagulant as that described by J u e r g e n s , although they found no characteristic behaviour in patients with hepatic affections. They did find an increase in "thrombin inhibitor", however, in cases of venous thrombosis and following pulmonary embolism (134). In none of their cases, however, was the clotting mechanism disturbed in such a manner as to result in an increase in clotting time. This anticoagulant may be identical with that described by S c h w a r z , W a n n e r and K o l l e r as early as 1951 (109); these authors then distinguished between so-called hepatic antithrombin and heparin, although K o l l e r and F r i t s c h y were still using the term "heparin antithrombin" in 1947 (67). This so-called hepatic antithrombin shows an increase especially in cases of extensive diffuse hepatic damage. The French authors have made no sharp distinction between heparin antithrombin and "antithrombine immédiate", which shows an increase in the case of affections of the liver; in his latest paper A l a g i l l e still merely refers to "héparine" (1).

In view of the data obtained in our case it can be stated that an unmistakable increase in clotting time does not occur until the γ-globulin values exceeds 4—5 g/100 ml. Cases showing increases to this extent are rare. Lack of systematic coagulation testing in these rare cases and in cases of hypergammaglobulinaemia in general, and especially the lack of cases with an increase in clotting time as a result of an increase in antithrombin-V, which is parallel with the increase in γ-globulins, probably explains why it has hitherto not been possible more precisely to define this antithrombin and also to distinguish it more sharply from heparin antithrombin.

Antithrombin-V is very probably a physiological antithrombin (in several preliminary experiments we succeeded in isolating a protein fraction with properties of antithrombin-V from normal serum γ-globulins only very slightly mixed with β-globulins).

The Clinical Significance of Antithrombin-V

Our experience has taught us that a "antithrombine immédiate", probably antithrombin-V shows in increase in very many patients with chronic inflammatory processes. Antithrombin-V has an anticoagulant effect and, as such, can afford protection against thrombo-embolic processes in many cases as an physiological anticoagulant.

In our opinion a decrease in antithrombin-V might also be an important factor in the aetiology of proliferative (stenosing) atheromatosis, which according to D u g u i d is based chiefly on recurrent thrombus formation (30).

Thrombo-embolic complications during treatment with ACTH and cortisone, and early severe atheromatosis associated with C u s h i n g ' s disease, could be partly based on a decrease in antithrombin-V; it should be pointed out that administration of ACTH or cortisone is normally followed by a decrease in "antithrombine immédiate" (not only in the case described).

The extent to which antithrombin-V is truly of importance in the pathogenesis of thromboembolic affections can only be established with certainty on the basis of the results of further systematic investigations.

Summary

A report is represented on a 44-year-old patient suffering, since 1938, from very slowly progressive rheumatoid arthritis. Haemorrhagic manifestations have been seen since 1951 (large cutaneous and muscular haemorrhages, microhaematuria and macrohaematuria, possibly also articular haemorrhages). In addition to

an extremely marked increase in γ-globulins to values above 8 g/100 ml (γ-globulins with a normal sedimentation constant S 7) a circulating anticoagulant was demonstrable, which is held responsible for the marked increase in clotting time, "prothrombin" time and thrombin time. The hypothesis is forwarded that this is a physiological anticoagulant showing a marked increase. Since it is different from the four antithrombins described by S e e g e r s it is referred to as antithrombin-V. Antithrombin-V occurs both in the plasma and in the serum and appears to be bound to the (β)γ-fraction. It is a thrombin inhibitor which, unlike antithrombin-II, has no direct effect on thromboplastin and thrombin formation. Antithrombin-V cannot be neutralized by protamine sulphate; it is heat-stable, not dialysable and not adsorbed onto BaSO₄. Thrombelastography made it possible clearly to demonstrate that an increase in antithrombin-V is associated with a marked increase in clotting time but causes no pathological course of clot formation.

Therapeutic results obtained with ACTH and cortisone are favourable: the activity of antithrombin-V decreases parallel with a decrease in γ-globulin values, and the clotting time is normalized. The patient has received, during the past 16 months, oral cortisone treatment (25 mg thrice daily), and is at present free of complaints, although clinical and laboratory findings show a gradual increase in symptoms respectively γ-globulin values with a slight increase in clotting time.

The possible significance of the antithrombin-V activity in the protection against thrombo-embolism is briefly mentioned.

Résumé

On rapporte le cas d'un malade de 44 ans, qui souffre depuis 1938 d'une arthrite rhumatismale lentement progressive. Depuis 1951 il apparut une diathèse hémorrhagique (hémorrhagies musculaires et cutanées, hématuries micro- et macroscopiques, hémarthroses probables). A part d'une augmentation notable des gammaglobulines jusqu'à des valeurs dépassant 8 g/100 ml (gamma-globulines avec une valeur normale d'ultracentrifugation de 7 unités Svedberg), on a pu mettre en évidence dans le sang une substance anticoagulante responsable de l'allongement prononcé du temps de coagulation, de „prothrombine" et de thrombine.

On émet l'hypothèse de l'hyperproduction d'un anticoagulant physiologique. Mais comme cette substance n'est pas identique à un des 4 antithrombines décrites par S e e g e r s, on l'appelle „antithrombine-V". L'antithrombine-V se trouve aussi bien dans le serum que dans le plasma, et elle semble être liée à la fraction gamma.

Il s'agit d'un inhibiteur de la thrombine qui, au contraire de l'antithrombine-II, n'a pas d'influence directe sur la formation de thromboplastine et de thrombine. L'antithrombine-V ne peut être neutralisée par le sulfate de protamine: elle est thermostable et non dialysable; enfin, elle n'est pas adsorbée par le sulfate de barium.

Grâce au thromboélastographe, on a pu mettre en évidence une nette augmentation du temps de coagulation (due à l'antithrombine-V), sans que l'élasticité du caillot semblât être influencée. Au point de vue thérapeutique, l'action de l'ACTH et de la cortisone paraît favorable: l'activité de l'antithrombine-V diminue parallèlement avec le taux des gamma-globulines; on assiste à une normalisation du temps de coagulation. Pendant les 16 derniers mois, le malade reçut une dose d'entretien de cortisone à raison de 3 × 25 mg par jour; c'est ainsi qu'il ne se plaint de rien, bien que les résultats cliniques et de laboratoire mentionnent une légère rechute de la symptomatologie, surtout en ce qui concerne les gamma-globulines et le temps de coagulation.

Enfin, on discute brièvement le rôle probable de l'antithrombine-V dans la protection contre des accidents thrombo-emboliques.

Zusammenfassung

Es wird der Fall eines 44jährigen Patienten, der seit 1938 an einer sehr langsam fortschreitenden rheumatoiden Arthritis leidet, geschildert. Hämorrhagische Erscheinungen wurden seit 1951 beobachtet (ausgedehnte Haut- und Muskelhämorrhagien, Mikro- und Makrohämaturie, wahrscheinlich auch artikuläre Blutungen). Außer einer beträchtlichen Zunahme der γ-Globuline auf Werte über 8 g/100 ml (γ-Globuline mit einer normalen Senkungskonstante von 7 Svedberg-Einheiten) wurde ein zirkulierendes Antikoagulans gefunden, welches für die ausgeprägte Zunahme der Gerinnungszeit, der „Prothrombin-" und Thrombinzeit verantwortlich gemacht werden kann.

Es wird die Hypothese aufgestellt, daß es sich um ein physiologisches, eine deutliche Zunahme zeigendes, Antikoagulans handelt. Da es mit keinem der vier von S e e g e r s beschriebenen Antithrombinen identisch ist, wird es als Antithrombin-V bezeichnet. Antithrombin-V kommt sowohl im Plasma als auch im Serum vor und scheint an die γ-Fraktion gebunden zu sein.

Es ist ein Thrombin-Inhibitor, welcher im Gegensatz zu Antithrombin-II keinen direkten Einfluß auf die Bildung von Thromboplastin und Thrombin hat.

Antithrombin-V kann durch Protaminsulfat nicht neutralisiert werden, es ist hitzebeständig, nicht dialysierbar und wird an Bariumsulfat nicht adsorbiert.

Die Thrombelastographie ermöglicht deutlich darzustellen, daß eine Zunahme von Antithrombin-V mit einer starken Zunahme der Gerinnungszeit verbunden ist, jedoch keinen pathologischen Ablauf der Gerinnselbildung verursacht.

Therapeutische Ergebnisse mit ACTH und Cortison sind günstig: die Antithrombin-V-Aktivität nimmt parallel mit einer Abnahme der γ-Globulin-Werte ab, und die Gerinnungszeit wird normalisiert. Der Patient erhielt in den vergangenen 16 Monaten perorale Cortisongaben (1 Tablette à 25 mg 3mal täglich), ist momentan beschwerdefrei, obwohl klinische und Laboratoriumsbefunde eine allmähliche Zunahme der Symptome, u. a. der γ-Globuline, und eine leichte Zunahme der Gerinnungszeit zeigen.

Die Möglichkeit einer Bedeutung der Antithrombin-V-Aktivität als Schutz gegen Thrombo-Embolien wird kurz erwähnt.

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