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FIBRINOLYSIS

If normal blood is diluted in a suitable buffered medium and then clotted, the clots can be observed to disappear over a period of hours. This phenomenon may be seen either in blood or plasma. The clot, which has a solid appearance, starts to fragment and ultimately lyses completely. This is due to the fact that normal human and animal plasma and serum contain a globulin, plasminogen which, in the presence of activators, is rapidly converted to plasmin, a proteolytic enzyme. This enzyme is able to attack various substrates such as gelatin, casein, fibrinogen and most important of all—fibrin. It is present in the blood in such a concentration that when fully activated it would be capable of digesting the total fibrinogen of the body in a few minutes.

Acute and chronic thrombo-embolic vascular disease is an important cause of human illness, and the possibility of its treatment by measures designed to produce dissolution of the causative thrombus or embolus by enzymatic means arouses exciting possibilities. Cliffton[1] has now gone so far as to say that the rapid dissolution of intravascular clots or thrombi by fibrinolytic activity is an accomplished fact. Progress in this field has been rapid as was clearly demonstrated[1] in a recent number of the journal *Angiology*.

In vitro experiments have shown that fibrinolytic activity can be induced in the blood by a number of different processes. Normal plasma, for instance, when treated with bacterial filtrates, develops powerful fibrinolytic and proteolytic activity. Streptokinase (SK), which is the name given to an extracellular product of haemolytic streptococcal metabolism, is capable of activating precursor substances in plasma and inducing fibrinolysis. It has thus been used in the lysis of extravascular fibrin clots in man, e.g. in fibrinous pleural effusions. However, the intravascular use of SK and SK-activated substances raises some difficulties.

The physiological process by which the enzyme becomes available for action *in vivo* is still in dispute. There are two main theories. Both agree that a pro-enzyme, plasminogen, exists in the plasma and this is activated to plasmin which is the proteolytic (fibrinolytic) enzyme. According to one theory SK or a similarly acting substance activates plasminogen to plasmin while additional SK reacts with plasmin to form an activator complex. Alternatively it is postulated that there is already a pro-activator present which combines with SK to form activator, and this activator combines with plasminogen to form plasmin. The dispute centres round the question: does SK activate or is a SK=enzyme combination the activator?

Naturally such a potentially powerful system could not be expected to exist in the blood without an equally powerful system of inhibitors; this proteolytic system needs to be uninhibited or 'free' if it is to act. It may be interfered with at least at three levels:[2] (1) SK may be neutralized by its specific antibody and so be unavailable for activity, (2) the activator may be neutralized by an inhibitor in the plasma, and (3) plasmin itself may be inhibited by another plasma substance.

The therapeutic applications of all this work is still in its infancy. There are at least two ways in which fibrinolysis may be stimulated. Either plasminogen of plasma can be activated to plasmin *in vitro*, purified, concentrated, and then injected, or else the patient's own fibrinolytic system can be activated *in vivo*. A number of studies relating to both types of approach to this problem have been recorded in the literature. For example, commercially available plasmin from streptokinase-streptodornase (SK-SD) activated human plasminogen has been injected intravenously in patients with venous thrombosis, arterial thrombosis and thrombosis of the central retinal vein.[1,3-7] The results are better in the treatment of venous thrombosis than in the treatment of arterial thrombosis, but improvement has occurred in both. Unfortunately, side-reactions, e.g. fever, chills, cyanosis, hypotension, leucopenia and thrombocytopenia occur. Some of these have been controlled by antipyretic and antihistaminic drugs and may be due to excess of SK-SD. The side-effects can be diminished by using less activator or by the preparation of more highly purified extracts, and have not been a real bar to extensive use of this preparation.

The patient's own fibrinolytic system has been activated by the injection of protein-free pyrogenic lipopolysaccharides.[8] Results were 'encouraging' especially in cases of venous thrombosis, but once again there were unpleasant and severe side-effects not completely controlled by antipyretics. Alternatively, a purified form of SK has been injected intravenously.[2,9,10] It was found that the dose of SK used was critical if re-formation of the clot was to be avoided. As a preliminary step it was necessary to give an initial, or priming dose just sufficient to neutralize the circulating SK antibody and inhibitor. Unfortunately the amount of these inhibitors varied considerably from patient to patient. Once neutralization had been achieved the use of different quantities of SK had different effects. Small amounts of SK resulted in moderate or large amounts of circulating plasmin. This resulted in a marked lengthening of the prothrombin time and depletion of fibrinogen with potentially serious effects to the patient. After the use of large amounts of SK, free SK remained in the plasma and there was depletion of plasminogen and in some cases actual re-formation of a previously lysed clot. The best results were obtained when the SK dosage was so adjusted as to generate small amounts of both SK and plasmin in the circulating blood. In this way consistent and reproducible intravascular clot lysis could be produced and re-formation of the clot did not occur. Side-reactions did occur but these were not unduly troublesome.

All this work points to a potentially powerful therapeutic tool. It is clear that the techniques are not as yet sufficiently standardized for general application. The use of fibrinolytic enzymes intravascularly, except under carefully controlled conditions, might be dangerous and should not yet be recommended. Results so far have been far better in the treatment of venous rather than arterial thromboses and have been better in the first 48 hours after the formation

of thrombus than subsequently. The treatment may be much more hazardous than the disease and there is evidence that immune responses may develop which might preclude further treatment along these lines. These principles cannot yet be successfully applied on a large scale in the treatment of such conditions as coronary or cerebral atheroma, but this type of treatment may not be long delayed.

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'N HOSPITAAL SONDER GERASE

Dit is interessant om daarop te let hoedat, by die opstel van die beginsels van hospitaal-beplanning en -konstruksie, die probleem van gerase in die verlede verwaarloos is. Van al die klagtes wat pasiënte oor hospitale opper (en dit is ook waar van goedgesinde, welwillende pasiënte wat in spesiale hospitale en opleidingshospitale verpleeg word) is dié oor gerase seker die mees konstante. Die soort gerase wat die meeste voorkom en die grootste ongerief veroorsaak vir pasiënte wat ernstig siek is, is die volgende:

Daar is, om mee te begin, gerase wat ontstaan as gevolg van die interkommunikasiestelsel in die hospitaal. By sommige hospitale is die skrikwekkende uitsaai-stelsel nog in gebruik. Dwarsdeur die dag en nag word die name van dokters wat êrens benodig word op so 'n manier uitgeroep dat daar geen twyfel kan bestaan oor die feit dat die geraas—want vir die pasiënt is dit niks anders nie—tot in elke hoekie deurdring. Oor die meriete van die verskillende soorte kommunikasiestelsels wil ons ons nie nou uitlaat nie. Dit is alreeds by 'n vorige geleentheid bespreek.[1] Wat ons egter wil benadruk is dat hierdie soort nimmereindigende geraas sonder twyfel 'n negatiewe en versteurende faktor is.

As deel van die kommunikasiestelsel is daar ook die telefoon. Pasiënte wat dit so ongelukkig tref om 'n kamer te hê iewers in die nabyheid van 'n telefoon, word dikwels dwarsdeur die dag en nag aan die luigeluid blootgestel, sowel as aan die gepraat van persone wat die telefoon gebruik.

Meganiese hulpmiddels in die hospitaal, soos byvoorbeeld hysers, stootstoele, trollies, apparaat, en kombuisgereedskap is verantwoordelik vir 'n groot deel van die versteurende geraas wat vir pasiënte met hoofpyn of prikkelbaarheid soms ondraaglik word. In sommige hospitale met 'n ouere soort uitrusting op hierdie gebied, vorm die geklap en gekrys van hyserbakke en deure so 'n ontstellende geraas dat dit nouliks denkbaar is dat dit deur die hospitaaloutoriteite gedoog word.

Onverantwoordelike geskerts en gepraat en gelag deur lede van die verplegingspersoneel sowel as deur lede van die publiek dra dikwels by tot die las van gerase waarmee die pasiënt opgesaal word. Ook is hospitale dikwels (veral in die grotere stede) op plekke gebou waar die verkeersgerase onvermydelik 'n versteurende element vorm.

Die meeste van die gerase waarna ons hierbo verwys het, kan deur goeie beplanning uitgeskakel word of deur goeie administrasie voorkom word. Aan die Universiteit van Münster in Wesfalië is byvoorbeeld onlangs 'n modelhospitaal gebou wat geheel en al klankdig is. Die hospitaal is so gebou dat alle soorte klanke geabsorbeer word. Alle moontlike bronne van gerase is by die beplanning en konstruksie van die hospitaal in ag geneem sodat die uiteindelike produk as 'n tegniese en argitektoniese model beskou kan word.

Dit is weliswaar die geval dat hierdie hospitaal, wat eintlik die oor-, neus- en keelafdeling van die Universiteit van Münster is, ontwerp is met die oog op spesiale oornavorsing. Ook het dit 'n groot som geld gekos om te bou en dit het drie en 'n half jaar geneem om die gebou te voltooi.

Daar kan nie orals oor die wêreld modelhospitale van hierdie aard gebou word nie. Maar, en dit is hierdie aspek van die probleem van hospitaalbehandeling wat ons hier wil beklemtoon, 'n voorbeeld soos hierdie dui op wat wel gedoen kan word om die gerief en die geluk van die pasiënt te verseker, bowe en behalwe die spesifieke mediese behandeling wat hy kry. Dat elke pasiënt nie net 'n geval is nie, maar ook 'n mens, met al die gewone menslike swakhede en met 'n vermeerderde prikkelbaarheid gedurende tye van ernstige siekte, kan nooit sterk genoeg beklemtoon word nie.

1. Van die Redaksie (1958): S. Afr. T. Geneesk., **32**, 907.