South African Medical Journal : Suid-Afrikaanse Tydskrif vir Geneeskunde

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FACTOR VII

It is a curious fact that the serum which remains after blood has clotted is rich in coagulation factors. This was noted in 1912 by Bordet and De Lange[1] who collected bird and rabbit blood which was relatively free of contamination with tissue juice or platelets. The blood clotted slowly and the serum contained large amounts of prothrombin. Addition of platelet extract at this stage yielded thrombin more rapidly than in the corresponding plasma. In 1924 Schofield[2] found that a haemorrhagic disease of cattle resulting from inclusion of spoiled sweet clover (which contains dicoumarol) in the fodder could be helped by the injection into the animal of normal serum. Owen and Bollman[3] showed that the prolonged one-stage prothrombin time of the plasma of dogs treated with dicoumarol could be corrected *in vitro* by the addition of a small amount of normal serum. Jacox[4] showed that the coagulant activity of brain extract was increased by incubation of the extract with normal serum. From these and other observations it became obvious that serum contained a factor or factors active in prothrombin conversion. This 'factor' has been given a bewildering variety of names, e.g. prothrombin conversion factor, serum prothrombin conversion accelerator (SPCA), co-thromboplastin, convertin, stable component, factor VII and others. We propose to use the term factor VII to refer to this factor and to its possible plasma precursor. As several of its names indicate, this factor seems to be of importance in the conversion of prothrombin to thrombin. In addition to this factor, serum also contains another factor—Christmas factor. This is best shown by the thromboplastin-generation test of Biggs and Douglas.[5] This factor is missing in serum from patients with Christmas disease and is present in patients with haemophilia.

Quick's one-stage test for 'prothrombin efficiency' is widely used in the control of anticoagulant therapy. Two rare causes of abnormality of this test are fibrinogen deficiency and the presence of inhibitors, such as heparin, in the plasma. In most cases the cause of the long one-stage prothrombin time is a deficiency of one or more members of the 'prothrombin complex'. These are factors V and VII and prothrombin. Factor-V deficiency is only rarely encountered, while deficiency of factor VII and prothrombin deficiency are much commoner. Serum contains little if any prothrombin or factor V since they are consumed during clotting of the blood. If the long one-stage prothrombin time is shortened by the addition of normal serum, then it is probable that factor VII is a missing factor in the plasma. Plasma treated by adsorption with aluminium hydroxide or barium sulphate contains little or no prothrombin or factor VII and will usually not shorten the prolonged one-stage time of this type of plasma. Patients on anticoagulant therapy (dicoumarol or phenindione) have a prolonged one-stage prothrombin time due to a combined deficiency of prothrombin and factor VII. Patients with obstructive jaundice, steatorrhoea or liver disease commonly have defects of this type, while similar varieties may occur spontaneously in patients presenting as 'bleeders' since birth—so-called 'idiopathic hypoprothrombinaemia' or 'congenital factor-VII deficiency'.

Study of all these varieties of bloods has shown that the picture is even more complicated than was at first realized. In 1953 Biggs, Douglas and Macfarlane[6] tested the serum of patients treated with the coumarin drug tromexan, and found all samples gave abnormal results when used to replace normal serum in the thromboplastin-generation test. They concluded that factor VII was necessary for thromboplastin generation. This conclusion was made questionable by the findings that serum samples from certain patients with congenital factor-VII deficiency (as judged by one-stage prothrombin-time tests) have normal thromboplastin formation[7-9] and that the defect caused by the coumarin drugs is very complex, many possible factors being involved. It has been suggested that in addition to factor VII a new factor (factor X[10,11]) and even Christmas factor[8,9,12] may be deficient in these cases. Biggs[9] and Greig and Tattersall[13] also presented evidence that there seemed to be at least 3 coagulation factors present in normal serum.

Some of the differences encountered by various workers have been resolved by the finding that sera from patients treated with different coumarin drugs have different levels of Christmas factor: Tromexan causes a rapid and marked fall in Christmas factor whereas dindevan and possibly marcoumar have much less effect on Christmas factor. In mild cases of obstructive jaundice and/or vitamin-K deficiency, Christmas factor may be little affected, whereas it is sometimes markedly reduced in severely affected cases.[9]

The picture became even more confused when it was found that blood specimens from patients with 'congenital factor VII' deficiency were, in some cases, mutually correctable, thus also implying the presence of an additional factor.[14] There are apparently 2 groups of cases both presenting with a long one-stage prothrombin time (when brain thromboplastin was used) correctable by normal serum,[15] viz.:

Type A (pure factor-VII deficiency). Here there is (1) normal thromboplastin generation and (2) normal one-stage prothrombin time with Russell viper venom (stypven) instead of brain thromboplastin in the Quick test.

Type B (deficiency of the so-called 'Stuart-Prower' factor, which is probably identical with Koller's factor X). These cases have (1) abnormal thromboplastin generation and (2) abnormal one-stage prothrombin time with stypven.

By electrophoresis of human serum Bergsagel[16] and Denson[15] showed that factor VII migrated with the β globulins (as Christmas factor did) while the 'Stuart-Prower' factor migrated with the α globulin, thus confirming the presence of at least 3 factors in serum. Some patients were found belonging to type A, some to type B, while some lack both factors. The original case of 'Prower' defect apparently lacks both 'Stuart-Prower' factor and factor VII!

It is possible also that these defects may even occur together with other varieties of bleeding disorder.[9]

These findings help to explain some of the findings in the sera of patients on anticoagulant therapy. Not only is the type of drug used important but a time factor is also involved. The defects which arise appear to be as follows: (1) In the first few days of treatment a reduction in factor VII only, which is associated with a fall in the one-stage prothrombin time if brain thromboplastin is used but not if stypven is used as a thromboplastin. (2) Later 'Stuart-Prower' factor is reduced, and Christmas factor also.

In 'dindevan plasma', therefore, a mixed variety of defect occurs, depending on the duration and intensity of therapy. The whole subject is a complex one but it does seem as if there are at least 3 factors in serum which affect blood coagulation, viz. Christmas factor and two others in the 'factor-VII' group—one of these might be called factor VII and the other 'Stuart-Prower' factor—the last name, incidentally, being derived from the surnames of the patients presenting with the disease, and not from the investigators.

In the following table a summary is given of some of the facts presented above:

Test	*'Factor-VII' deficiency*		*Christmas-factor deficiency*	*Anticoagulant therapy*	
	Factor VII defect	*'Stuart-Prower' defect*		*Early*	*Late*
One-stage prothrombin time (Quick's test)					
(*a*) With brain thromboplastin	Abnormal	Abnormal	Normal	Abnormal	Abnormal
(*b*) With Russell viper venom (stypven)	Normal	Abnormal	Normal	Normal	Abnormal
Thromboplastin generation test	Normal	Abnormal	Abnormal	Usually normal but sometimes abnormal	Abnormal

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BEGINSELS BY DIE GENEESKUNDIGE OPLEIDING

Gedurende die laaste aantal jare word die beginsels wat aan die grond van die geneeskundige opleiding lê, en behoort te lê, dwarsoor die wêreld druk bespreek. Die struktuur van die mediese kennis het oor die afgelope aantal jare onerkenbaar verander. Daarby het ook die patroon van ons gemeenskapslewe 'n radikale verandering ondergaan. In die lig van hierdie feite word dit allerweë gevoel dat die beginsels van mediese opleiding en onderrig ook in wesenlike heroorweging geneem moet word.

Ook in ons land het die nuwe rigtings en beklemtonings neerslag gevind. Aan ons ouere, gevestigde mediese skole het al meer stemme oor die vereistes van die omvattende medisyne opgegaan. En omdat daar beleidsbesluite oor die doelstellinge en metodes van onderrig aan ons jongere mediese skole geneem moes word, is dit veral hier waar ons die stemme sterk en duidelik verneem het. So het prof. H. B. Thom byvoorbeeld, Rektor van die Universiteit van Stellenbosch, in die *Tydskrif* van 24 Maart 1956 'n volledige uiteensetting gegee van hierdie nuwe benadering soos hy dit in Kanada en Brittanje teengekom het en soos hy dit graag aan die mediese skool te Stellenbosch toegepas sou wou sien. Die mediese skool van die Universiteit van Natal het reeds al ver gevorder—miskien verder as enige ander mediese skool—in die toepassing van die basiese beginsels van hierdie nuwe benadering. En elders in hierdie uitgawe van die *Tydskrif* plaas ons 'n onlangse lesing van prof. H. W. Snyman, hoof van die departement van interne geneeskunde van die Universiteit van Pretoria, waarin aangetoon word dat die nuwe benadering ook op Pretoria wortel geskiet het. Wat is nou die essensie van die nuwe benadering? Ons sou dit baie kortliks en sketsmatig in die volgende punte kon opsom:

1. *Omvattende medisyne.* Dit word gevoel dat die geneeskundige onderwys al meer los geraak het van die samelewing aan die een kant en van die kulturele universiteit aan die anderkant—dat die mediese opleiding byna te veel tegniese opleiding geword het. Die punt is dat die menslike opvatting gevaar geloop het om deur kliniese oorwegings volstrek oorskadu te word. Die pasiënt met al sy behoeftes as mens moet net so belangrik bly soos sy siekte; trouens, sukses by die behandeling van sy siekte staan dikwels in noue verband met die suksesvolle hantering van die pasiënt as mens. Daarom moet die mediese opleiding hiermee rekening hou.

2. *Gesinsversorging.* Die opvatting dat gesinsversorging altyd 'n groot deel moet bly uitmaak van die hantering en behandeling van siek mense is reeds al oud, maar dit word nou weer orals opnuut beklemtoon. Die pasiënte wat vir mediese onderwys die kliniese materiaal moet uitmaak, is nie net in opleidingshospitale te vinde nie. Studente moet, saam met maatskaplike werkers, 'n groter insae kry in die totale agtergrond van hulle pasiënte. Eintlik is dit weer die benadering en gesindheid wat hier van oorwegende belang is, nl. dat die mens, en nie net sy siekte nie, in gedagte gehou moet word.

3. *Koördinering van leergange.* Dit word al meer gevoel dat die basiese vakke van die medisyne nie in waterdigte kompartemente gedoseer kan word nie, maar dat hulle telkens sover moontlik gekoördineer en geïntegreer moet word en dat onderrig in die medisyne al meer om die funksie van die orgaan, maar veral van die hele mens moet wentel.

4. *Etiologie van siekte.* Anders as by die benadering van die verlede, het die opvatting van die enkelvoudige veroorsaking van siekte nou plek gemaak vir die opvatting van meervoudige veroorsaking. Daar is nooit net een oorsaak van 'n siekte nie, daar is gewoonlik verskeie oorsake en dikwels baie. By beskouing van hierdie nuwe opvatting van die veroorsaking van siekte speel oorwegings aangaande die voorkoming van siekte en die voorbehoedende medisyne 'n groot rol.

Om saam te vat sou ons kon sê dat hierdie nuwe beklemtonings in werklikheid beteken dat suksesvolle mediese praktyk in die moderne wêreld nie net die toepassing van tegnies-wetenskaplike beginsels behels nie, maar dat dit ook 'n kuns is wat met oorleg en op die basis van 'n gesonde lewensuitkyk en idealisme uitgeoefen behoort te word. Die feit dat die mediese praktyk ook en veral 'n lewenskuns is, maak dit egter nie minder noodsaaklik vir die dokter om sy basiese wetenskaplike en kliniese kennis suiwer en grondig te verkry en te bewaar nie. Trouens, omrede van die snelle en geweldige uitbreiding van die aard en omvang van die mediese kennis, word volgehoue nagraadse opvoeding al meer 'n groot morele verpligting vir die dokter. Elke dokter moet gedurig bly leer sodat sy pasiënte gelukkig kan bly lewe.