

THE JOHNS HOPKINS HOSPITAL

BALTIMORE, MARYLAND 21205

Department of Pediatrics

March 6, 1986



Dr. Joshua Lederberg
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Dear Josh:

Thanks for the Haldane paper. I'd not seen it, nor would I have been able to find it here. It certainly reads like something modern.

I don't mean to omit Troland. Our library (in fact, both the medical and university library) lacks the American Naturalist as far back as 1917, but I've sent away for the paper.

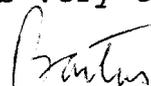
Apropos your remark, "But it is hard for me to believe this wasn't cleared up in the 40's." The enclosed table gives the chronology of the discovery of the factors, and two pages from an article by Macfarlane, also enclosed, show his confusion in 1951. I also read the other papers in the symposium reported in the same number of Blood as that of John Graham (1954). None showed any grasp at all of relationships between genes and proteins, and they were written by all the big wigs of the time, including Macfarlane, Quick and others. Graham's paper stands altogether apart from the others and must surely represent the first statement of gene-protein affinity in this field. It would be an interesting study to observe how the idea spread in the later 50's and 60's. A historical review of hemophilia published by Brinkhous in 1975 was no help; no emphasis was given to the genes. I wonder if the genetic idea helped Macfarlane to propose his cascade -- a model which gave coherence to the clotting mechanism. If Macfarlane clearly understood the first page of Graham's paper, he might easily have extended the idea to a series of proteins each specified by a gene and each a part of a pathway leading to a clot. Obviously, he got there somehow. I'd better look to see how. My guess is that the diffusion of the gene-clotting factor idea was slow and irregular; some of the participants in the elaboration of the ideas got it right away (in the 50's), others haven't got it yet. I don't know how much genetics is a part of the clotters' thinking today. For example, I don't know whether anyone has yet looked for polymorphisms that might account for minor variations in clotting -- maybe of significance in trauma or even myocardial infarction. Graham did find a mild hemophilia

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years ago which he called an allelic variant. Genetic analysis has helped in trying to understand a number of puzzling multifactor deficiencies (Sem. in Thrombosis and Hemostasis, 7, 112-167, 1981).

I'm enjoying this exchange very much. The history of ideas is the most interesting history.

Yours very truly,



Barton Childs, M.D.
Professor Emeritus

BC:ep

DATE	FACTOR NUMBER	REMARKS
PRE-46	I II III IV	Fibrinogen Prothrombin Calcium
1946	FACTOR V	FOUND IN A "HEMOPHILIC" WOMAN
1951	FACTOR VI	PROTHROMBIN CONVERSION ACCELERATOR
1951-1952	FACTOR IX	CHRISTMAS DISEASE
1955-1956	FACTOR XII	RATNOFF
	FACTOR XI	GRAHAM + BRINKHOUS (STUART FACTOR)
	FACTOR X	
1960-1962	FACTOR VIII	"ANTIHEMOPHILIC GLOBULIN" DISCOVERED IN 30'S.

1958 INTERNATIONAL CONGRESS - DECISION TO USE Roman NUMERALS.

FACTOR VI is MISSING

MAEFARLANE CASCADE PROPOSED IN LATE 50'S.

COHN'S FRACTION I WAS SHOWN IN THE 40'S TO CONTAIN AN ANTIHEMOPHILIC GLOBULIN.

Information obtained mainly from John Graham by telephone, 6 March, 1986