J Beam

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A Garrod

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Dear Josh:

Here's a more accurate table of the serial discovery of clotting factors taken from a paper of John Graham (Scand. Jour. Haematol. 7, 14-18, 1965). I think each was discovered (except I and II?) in patients with a genetic deficiency of a different factor. Macfarlane elaborated his cascade in 1964, not mentioning the genes (Nature 202, 498-499, 1964). He certainly didn't see the cascade as an expression of a genetic mechanism for the control of clotting. But since then several anti-coagulant factors have turned up, again discovered in genetically deficient patients, and both protein deficient, and abnormal molecular forms have been found for some. So, I think the gene-enzyme idea was helpful in constructing this homeostatic system; whenever someone was found to fail to clot or to clot too readily, a genetic defect in a protein was suspected. It seems that this idea (traceable in part to Garrod) is pretty well embedded in the thinking of medical investigators, if not of all medical practitioners.

But, however, desirable, it's too limiting, too categorical. The next phase in the advance in medical-genetic thinking is going to be more interesting, embracing the idea of "chemical individuality" first proposed by Garrod in his 1902 paper and fully matured in his second book (1931). To me, it's his most profound and interesting idea and it accommodates readily, as most medical thought does not, to the idea that each person gets sick in his own way, due in part -- often in large part -- to genetic differences. This trend started with the blood groups, the hemoglobins, haptoglobins, transferrins, HLA alleles and the idea of genetic polymorphisms, and it leads to conclusions about variation in disease and susceptibility to disease, as well as about other kinds of variation and evolution. It should help in understanding multifactorial inheritance, still more or less a black box, and seems to be leading to new ideas about prevention. I can't say I think much of this development is traceable to Garrod, but he was certainly the first to modernize the principle of diathesis as inborn susceptibility. Oddly, though, there's no special emphasis on prevention in his writing -- nothing

at all in "Inborn Factors," apart from immunization. I say oddly only because I think that having gone so far as to think of chemical merits and chemical defects, he might think of chemical ways to prevent expression of the latter. But no one in medicine in his time was much taken with prevention. They had no means to do it.

There's another way in which Garrod's emphasis on chemical individuality makes him a leader of thought -- even if without followers. He was certainly a reductionist, even though there's no evidence he participated in the contention of the time. Statements of two of the heavyweights are enclosed; they are taken from Fruton's "Molecules and Life," Wiley 1972 (a great book). I enclose also the last paragraph of "Inborn Factors" which states unequivocally Garrod's chemical, even molecular, view of life. It's hard to see what's left for vitalism in such a construction. I wonder if any physician ever was anything but a reductionist.

Yours very truly,

Barton Childs, M.D.
Professor Emeritus

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