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Dear Josh:

Thanks for yours of 12 and 26 Nov. and for the interesting enclosures. It seems to me that you've asked five questions. They are:

1) When did Haldane, Scott-Moncrieff, and S. Wright first refer to Garrod?

2) Did G. extrapolate from pathogenic mutant genes to the view that genes were the source of developmental information?

3) Does he ever say anything about the normal allele?

4) The 1:1 idea is a subset of the statement that the genes carry all the hereditary information. What were G.'s views on this?

5) Why was he asked to give the Croonian Lectures?

As to question 1, I haven't done the homework yet, but Haldane's "The Enzymes" (1930) doesn't cite Garrod, but Wright did cite him in his Physiological Reviews paper of 1941.

I looked up all the textbooks of Biochemistry in our library that were published before 1945. What I found is enclosed.

As you see, Garrod was mentioned, usually briefly, and without any perception that he had had a profound idea.

About questions 2-4. I've made a xerox copy of the chapter on chemical individuality from Garrod's later book "Inborn Factors in Disease," and you will see that he alluded to development and the information in the hereditary material. He knew about mutations which occurred in the "germinal cells," and he refers to recessive and dominant modes of inheritance, so he knew that man is diploid (presumably). But he never mentions the words gene or allele anywhere that I could discover. I've always thought his views of

genetics ambiguous; I don't really know what he thought. He never expressed any relationship between one gene and one enzyme. His 1:1 idea was 1 enzyme:1 inborn error. By 1931 all the physical basis work had been done so he could have used such words as gene or allele, but he didn't.

I suppose it is possible he thought the enzymes themselves were inherited. He says again and again that the molecular (i.e., protein) variation that he sees as the basis of chemical individuality is a reflection of "molecular groupings" in the germ cell. I don't know what he meant by that.

To me his major contribution is the idea of chemical individuality. He extrapolated from the inborn errors to all the rest of physical and chemical variation, emphasizing the differences in proteins between and within species, and, as he said, the differences between species are greater than those within -- foreshadowing Harris and Lewontin. But I think Olby might call all this "precursor disease" because many aspects of protein chemistry were unknown at the time. Even so, Garrod saw chemical individuality in relation to evolution, normal variation and disease -- including infections. Inanmuch as most medical people right now haven't yet got that message, I think it was an extraordinary insight whether in 1902 or 1931.

As for question 5, I think the answer is that he was a greatly respected clinician who did unusual things -- like working in the laboratory. Later he was appointed Regius Professor at Oxford, even though his ideas on chemical individualtiy were no more appreciated then than in 1908 when he gave the lectures. Other distinguished physicians of the time (Albutt at Cambridge, for example) didn't do any research at all, so Garrod stood out in that sense, even if his work wasn't understood in more than a limited sense. Also, just the idea itself of an absent enzyme causing albinism and cystinuria might have been regarded by some as of unusual interest. Even though the inborn errors weren't common conditions, the idea of a discrete "cause" of anything in those times must have hit some people as a nice contribution.

I am delighted with your interest and will report later regarding Wright, Haldane, etc.

Yours very truly,

Barton

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