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Genetic Drift

ADRIEN BLEYER: In the Right Place at the Wrong Time

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A goddess capricious is fame
You may strive to make noted your name
But she either neglects you
Or coolly selects you
For laurels distinct from your aim.

Good timing is very important. Jerome Lejeune had it, and Adrien Bleyer – through no fault of his own – did not. And that is why Lejeune, rather than Bleyer, is a household word in divisions of medical genetics.

By all accounts, though, Adrien Bleyer was a remarkable man. He was born in 1879, in St. Louis, and died there 86 years later. He received his medical degree from the Missouri Medical College in 1899, and after the then-customary two-year internship, he began a distinguished career in pediatric practice and teaching at the St. Louis Children's Hospital and the Washington University School of Medicine. He served as president of the St. Louis Pediatrics Society, director of the St. Louis Pure Milk Commission, editor of the Washington University Medical Bulletin, and captain of the children's bureau of the American Red Cross in France during World War I; in addition, the establishment of the first infant welfare clinic in the United States was credited to him. He was best known among his colleagues, however, for his interest in Down syndrome.

Bleyer's fascination with mongolism seems to have begun during the 1920s; certainly, this was an unusual pursuit for a middle-aged generalist-become-pediatrician. Yet, he studied the condition at first hand, researched it extensively, and published a number of papers on the subject. Considering that at the time and for years afterward, many prominent pediatricians did not accept Down syndrome as a genuine entity and the condition often went undiagnosed, Bleyer's observations, insights, and conclusions were nothing short of astonishing.

The first paper Bleyer published on Down syndrome was titled "The Occurrence of Mongolism in Ethiopians" [JAMA 84:1041–1042, 1925]. Lest Senator Proxmire rush forward to award the author a posthumous Golden Fleece, let me mention that "Ethiopian" was a common synonym of the time for "Negro," and that this paper and several others that followed it addressed the then-controversial issue of the relationship of race to Down syndrome. The question can be traced back to Langdon Down himself, who attempted to classify the mentally retarded on the basis of physical traits supposedly characteristic of particular ethnic groups; in addition to the syndrome that ultimately conferred upon him epo-

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nymic fame, Down also described forms of "imbecility" which he designated as Tartar, Malay, Negro, and American. This sort of association was given a good deal of credence for some time: The idea that degeneration in one's own race might be traced to some sort of mysterious pollution by another racial group fit well with the sentiments of the influential eugenicists of the day. F. G. Crookshank argued that Down syndrome, limited as he insisted it was to the whitest of the white, constituted a throwback or a reversion to a preglacial mongolian or premongolian ancestor-type [Crookshank, FG: "The Mongol in Our Midst." New York: E. P. Dutton & Co., 1931]. Bleyer strongly disputed this thesis, presenting evidence that Down syndrome had been unequivocally identified in members of all three of the basic racial groups, as well as in 31 ethnic subgroups and/or nationalities [Bleyer, A: Frequency of mongoloid imbecility; question of race and apparent influence of sex. Amer J Dis Child 44:503–508, 1932; Bleyer, A: Mongolism in a North American Indian. J Miss Med Assoc 33:13–14, 1936]. In addition, he believed that the persistence of a hidden deleterious ancestral gene was inconsistent with both a nondiminishing (and perhaps even an increasing) incidence of the condition, and the failure to reproduce by the affected individuals.

Bleyer also noted that most estimates of the prevalence of Down syndrome were based upon the rates found in older patients, often in those who had been institutionalized. He demonstrated an increased likelihood of early death from the condition, and predicted that with early and accurate diagnosis, the true prevalence (or incidence) would be considerably higher than was generally assumed [Bleyer, A: Theoretical and clinical aspects of mongolism. J Miss Med Assoc 34:222–227, 1937]. With time, of course, he has been shown to have been correct.

Most interesting and most striking of all, though, were the thoughts Bleyer presented in his 1934 paper, "Indications That Mongoloid Imbecility is a Gametic Mutation of Degressive Type" [Amer J Dis Child 47:342–348, 1934]. With no formal training in genetics and no laboratory expertise, this "common-clay clinician" (his own words) presented a logical, coherent, and highly accurate argument for a specific numerical chromosomal error as the cause of Down syndrome.

Bleyer began the definitive portion of his presentation with the following statement:

> Looking at mongoloid imbeciles is like looking at the stars; the more one looks, the more one sees. New things are always appearing, and the suggestion is aroused that much more remains hidden from view. Certainly the more one studies these persons, the less one is able to find anything normal about them.

Bleyer combined this thought – "that the entire body seems to be involved" – with the observation that dizygotic twins were invariably discordant for Down syndrome and monozygotic twins concordant, to conclude that it was likely that whatever produced Down syndrome did so "at the time of fertilization or even before."

With this in mind, Bleyer then reviewed the mechanism of meiosis in light of the knowledge of his time, and wrote that ". . . a disturbance in the structure or the function of the chromosomes . . . might elaborate itself into disease." He went on to say:

> There may be an unequal migration of the chromosomes to the poles of the germ cell during the reduction period which will result in a cell progeny having a number of chromosomes unlike the number present in the parent.

He analogized this hypothetical situation to that known to occur in the evening primrose,

where a meiotic error can produce a form of the plant with 15 rather than the normal 14 chromosomes, "a mutation which de Vries called degressive because it was defective and in natural surroundings was incapable of reproducing itself." At the conclusion of the paper, Bleyer reiterated his belief that mongolism might be due to "an alteration in the normal number of chromosomes," and stated:

> The human cell is a forty-eight chromosome cell. Whether in the mongoloid imbecile one is dealing with forty-nine or forty-seven, with fifty or forty-six or with some other number of chromosomes must be left to the cytologist, in whose field the richest prizes in genetics now seem to lie.

And there, of course, they lay for another quarter-century until another brilliant clinician, working in a little room without running water, and using a discarded microscope whose gears he had rehabilitated with silverfoil from a candy-bar wrapper, seized the day [Hsu, TC: "Human and Mammalian Cytogenics. An Historical Perspective." New York: Springer-Verlag, 1979, pp 38–41]. As to what Bleyer might have thought and felt at the time we can only speculate: After all, he was 77 years old and retired when Tjio and Levan cleared the way for the direct testing of his hypothesis. Time had put him out of the running. Yet, it is good to know he lived long enough to see his opinion verified in fact. I suspect that the echoes of Lejeune's well-deserved round of applause were clearly audible to Adrien Bleyer.

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