INVITED COMMENT

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Pallister–Killian Syndrome: Historical Perspective and Foreword

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There have been quite some changes since I first became aware of genetics. In high school biology in 1938 we were taught that there were 48 human chromosomes just as we were at the University of Minnesota from 1938 to 1944. But in other parts of the world human chromosomes had been of interest for some time.

Lionel Sharples Penrose and coworkers worked at the Royal Eastern Counties Institute for 7 years; they examined 1,280 patients with "mental deficiency"; took 400 family histories and examined 6,629 parents and sibs. He finished this work at Colchester in 1934 and published his first book based on that study when I was 13 [Penrose, 1934]. In 1939 he published a paper concluding that aging mothers were more apt to have a "mongoloid child," that birth order was significant and that "mongolism and some other malformations may have their origins in chromosome abnormalities." I was a pre-med sophomore at the University of Minnesota. Petrus Waardenburg had suggested this in, 1932 as did others including Raymond Turpin in France.

After sometime spent as a United States Army physician, my wife and I determined never to live in a large city again; we moved to Boulder, Montana in 1947 for a life of a general practitioner. Part of my practice included responsibility for the health and welfare of the patients at the state institution for the "feeble-minded," "retarded," "mentally deficient," "developmentally impaired," and so on. Penrose [1949] published the book that fell into my hands in 1956. Initially there were 487 patients in Boulder but as our program developed we peaked at 1,187 "residents." Eventually several thousand were studied here, around the state and especially at the Shodair Genetic Center in Helena during the last 7 years of our active medical life.

As a General Practitioner, my interest was in developing diagnostic tools, rehabilitation programs, chromosome labs, biochemical screening, autopsy and neuropathology studies, electroencephalography, brain scanning, the natural history of disorders, drug and vaccine trials, writing laws to enhance the care of our patients, screening newborn infants for treatable, and untreatable conditions. And especially in the wide use of consultants (many of the world's greatest human geneticists came to Boulder) was to better understand and to treat my patients. And while I began these efforts, changes were taking place in human chromosome knowledge.

In 1953 Murray Barr distinguished the Barr body, the resting X chromosome on the nuclear membrane of cat neurones, a subject he had been interested in since 1949 [Barr and Bertram, 1949].

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On December 22, 1955 Joe Hin Tjio, "working in the laboratory of Albert Levan at 2 in the morning" in Lund, Sweden demonstrated that the human normal chromosome number was 46. Levan had developed the techniques including the use of colchicine to improve metaphase spreads while studying plant cytology [Tjio and Levan, 1956].

Levan's improved cell culture methods soon spread; at Harvard University Benedikt F. Massel, interested in rheumatoid arthritis (RA) and rheumatic heart disease, attracted the attention of a young French woman, Marthe Gautier, with similar interests. Gautier was incidentally trained in tissue culture in his lab while growing cells from aortic tissue removed in surgery. Returning to Paris she set up the laboratory for Raymond Turpin to determine the chromosome number in Down syndrome patients. Turpin had obtained tissue samples from patients but since they had no photomicrograph they turned to Jerôme Lejeune for the photography [Gilgenkrantz and Rivera, 2003].

Lejeune had been interested in the chromosomes of Down patients for some time and had made an oral presentation regarding the extra chromosome in 1958 at an English seminar and now the three collaborated in the famous 1959 publications demonstrating the extra 21 chromosome as cause of Down syndrome (Lejeune commented the extra chromosome appeared to be one of the smaller Gs or the 22nd pair) [Lejeune et al., 1959a,b]. By convention it has been agreed to call it the 21st pair.

In 1959 at the Hartford Connecticut meeting of AAMD (American Association on Mental Deficiency—now the AAIDD—American Association of Intellectual and Developmental

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FIG. 1. Dr. Philip D. Pallister examining a child with PKS at the first PKS Family Meeting held in Philadelphia in 2006.

Disabilities) I critiqued a joint paper by George Tarjan and Linus Pauling suggesting "mongolism" was an "enzyme defect" citing Lejeune's discovery. My comments were not well received and they apparently never published their paper.

Familiar with these developments because of my work with the intellectually impaired (I took care of more than 300 Down syndrome patients in Boulder and elsewhere) I desperately needed to develop cell culture capability in Boulder. An integral part of this effort was the enlistment of my friend and colleague, pathologist J. Allen (Al) Miller. In the fall of 1962 I attended a meeting in Spokane to learn all of the steps in culturing and harvesting lymphocytes and tried to interest Al in the process. He was not inclined until a few months later in the winter of 1963 when he attended an American Society of Clinical Pathology meeting in Florida—three out of 5 days were spent on chromosomes and cell culture techniques.

Al went to East Germany (communist at the time) to secure the Lindhof camera and Zeiss-Ikon microscope we needed to photograph the karyotypes. From there he went on to London where he visited Penrose for advice and encouragement.

The camera used Polaroid plates and it took minutes to make an exposure. A lens for the scope to correct for aberrant colors and lens curvature (apochromatic-planochromatic lens) was required. The Butte parents group donated the money for that lens. (Art Westwell, then Administrator at the Boulder "school," was setting up local and regional AAMD and NARC [National Association for Retarded Citizens] groups all over the Rockies.)

We set up the equipment in the old St. Peter's Hospital in Helena in an unused toilet of the old resident nurses' quarters where Al operated the hospital laboratory. The floor was wooden and the various refrigerators and equipment shook the building when they started up, blurring our exposures (up to $1^1/_2$ min or more exposure time), so we did most of that work on weekends when we could turn off the interference. The developing tanks were set on boards over the toilet and the tub. We were soon karyotyping in Boulder with few culture failures. From that time on we prepared lymphocyte chromosomes on each new admission to the institution.

We delineated several syndromes in those years, each with a special story behind the discovery. Some resulted from solid, basic medicine, physical exams, and histories; some were enlightened by laboratory work; all along, just plain luck—serendipity if you will—played a part.

Because of their similarity in appearance, I always thought our first two Pallister–Killian syndrome (PKS) patients had the same condition. They had several minor anomalies (aside from their profound intellectual disability) but their so-called "coarse" appearance suggested they had a storage disease, especially since lymphocytic chromosomes had been repeatedly apparently normal. Many biochemical disorders were being widely investigated here and elsewhere but we were unable to determine the cause of these two patients' conditions using all of our new modalities. We had learned to store tissues for future diagnoses as techniques developed even making a diagnosis of Sanfilippo disease (mucopolysaccharidosis (MPS) Type IV-A) when the disorder was first described using autopsy tissues from sisters who had died 10 years earlier.

Staff pediatric geneticist Gerry Miyazono, who had been trained by Arno Motulsky, accordingly collected skin samples and sent them to Lorraine Meisner in Madison WI to store for future use. Lorraine routinely karyotyped all cell cultures she stored and the isochromosome was discovered.

I had met John Marius Opitz in Madison in the spring of 1965. Impressed by his teaching ability and knowledge I prevailed upon him to come to Boulder as a teacher and consultant. Starting in the winter of 1966 John and his post-doctoral student, Jürgen Herrmann, worked here several times a year (M. Michael Cohen Jr and Bob Gorlin dubbed us the "Wisconsin team"). We first published the two cases in 1976 misidentifying the isochromosome as an F Group (20) chromosome by fluorescent staining [Pallister et al., 1976]. In our definitive article in 1977 Uta Franke and Lorraine Meisner identified it as isochromosome 12p (while Rafael Elejalde held it was a supernumerary 12 with a partially deleted long arm) [Pallister et al., 1977]. Opitz and Kaveggia recognized the third case (J.G.) in Central Colony, WI in 1977; he was one of 11 cases reported by Reynolds et al. [1987].

Teschler-Nicola and Killian [1981] reported a case in an infant and republished the same case in 1983 [Killian et al., 1983].

So here is serendipity:

Debra was admitted at age 12; 2 years later a male "attendant" forced an enema tube thru her vaginal vault tearing out the left uterine artery. I removed her uterus to save her life at 5:30 AM on a day in June 1971. If she had died we would not been able to make the comparison to the older male as possible MPS patients. If we had not been making the effort to determine the cause of the intellectual

disability in each of our patients, we would not have looked to future technology. If we had not harvested skin, a different tissue, Meisner would not have uncovered the isochromosome. If Opitz and Herrmann had not seen these two patients they would not had made the physiognostic connection to the third. So much for the scientific method!

It is not enough to collect some cases and write an article and perhaps discover a ''new'' syndrome. We must do more; we must at least act like physicians. The purpose of our investigations should be to delineate the disorders, study the natural history, the basic biology, all in order to improve the lot of the patients and their families. We often know very little about the brains, the neurophysiology, and pathology of most of the conditions we describe. Our oldest Pallister–Killian patient died when he was 50; on autopsy he had adrenal cysts and atrophy, renal cysts, and no testes. His brain was lost between Boulder and Wisconsin but we knew he had dilatation of the anterior horns. The severe ''coarsening'' was surely aggravated by Dilantin which also attacks the cerebellum. I have never seen the results of another PKS autopsy and sadly of no competent neuropathology study.

Several parents groups, starting with Marianne Haven's in 1991, have been organized in England, Italy, etc. and the largest, PKS Kids, in the United States. These families, asking for help, are bringing health professionals together to study their kids. Ian Krantz and his co-workers at the Children's Hospital of Philadelphia have examined over 60 patients in depth—including detailed physical and neurological exams, developmental evaluations, and medical and family histories. We know about smaller and smaller parts of chromosomes, loops and how they are read. But we do not know how our patients' dendritic spines look. So here is a review of what they have found and recommend to date. It is a work in progress.

Try as we might, we failed to make a diagnosis of the cause of the intellectual disability in about 30% of our Boulder patients. But we knew, based on the studies here and elsewhere by Opitz, Herrmann, and myself, that at least two-thirds of those patients had minor (but important) anomalies, despite seemingly normal lymphocytic chromosomes. With advanced techniques we are now finding that about 20% of intellectual disability is caused by minor, usually ''unique,'' chromosome rearrangements. One of Willie's and my fifteen children, whose chromosomes were apparently ''normal'' three times, has such a chromosome change finally recognized in 2008 at age 48.

Victor McKusick once told me he too was a GP ''like you are, Phil.'' He called himself a genetic practitioner because he touched all branches of medicine. We need to approach our patients as GPs, reassessing, studying, following, and caring.

And such is the focus of these reports—studies in progress.

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