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Introduction: A Tribute to David L. Nanney, An Experimental Ciliatologist

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In one of David Nanney's papers he gives A. Lwoff credit for having "persuaded *Tetrahymena* to eat beef" by growing it in axenic culture in 1923. Similarly one may give David Nanney the credit for having "persuaded *Tetrahymena* to have sex, and to tell the whole world about it."

Vagn Leick
The University of Copenhagen

This issue of *Developmental Genetics* honors David L. Nanney on the occasion of his retirement. He is the founder of *Tetrahymena* genetics and more than anyone has championed the ciliated protozoa as a rich source of phenomena for scientific investigation. His work has significance far beyond ciliate biology and touches on genetics, development and evolution. His legacy and impact, not only in this country but also abroad, reflect the diversity of his interests, some of which are represented in this volume. Interest in contributing to this special issue was so warm and intense that we had to a) limit the number of pages of each paper; b) focus only on researches that had a developmental genetics thrust, in some cases stretching its definition to the limit; and c) in a few other cases regretfully discourage interesting contributions (see Acknowledgments). In organizing the contents of this issue, we have attempted to recapitulate the evolution of Nanney's research interests. (A current bibliography appears at the end of this article; it includes Nanney's own papers, as well as those published by collaborators based on work conducted in his laboratory.) Articles in this issue have been grouped in sections in an order loosely described as follows: mating type and cell-cell recognition, nuclear fate and macronuclear differentiation in conjugation, genetic functions in the vegetative macronucleus, secretion, behavior, morphogenesis. Below we review, by necessity superficially, the development of Nanney's career to the present, interspersing our review with anecdotes contributed by collaborators and other scientific colleagues.

David Ledbetter Nanney is a native Virginian (born in Abingdon), but was raised in Wewoka, Oklahoma. He attended Oklahoma Baptist University in Shawnee, Oklahoma, where he majored in English. To this day he cannot resist correcting the grammar in everything he reads. For his students, writing a thesis was a lesson in the English language as well as a scientific process. His first professional experience with biology was as a graduate student at Indiana University, where he studied genetics with Tracy Sonneborn. He quickly became immersed in the lore, life style, and mating habits of *Paramecium aurelia*. His researches led to publications on mating type determination in *P. tetraurelia* (a model of nucleocytoplasmic interaction) and X-ray studies on paramecin and kappa in the same species.

After receiving his Ph.D. in 1951, and marrying Jean Kelly, he took up a position at the University of Michigan, where he became a tenured Associate Professor in 1956. There he began his life-long courtship of *Tetrahymena*, starting with the isolation of mating types, cytological studies of conjugation, and the genetic analysis of mating type determination in variety 1 of *T. pyriformis* (a species which he and his graduate student J.W. McCoy would later name *T. thermophila*). In 1959 he moved to the University of Illinois, where he was promoted to full Professor. He has worked there ever since, following his *Tetrahymena* star, collecting new strains and species wherever he has gone and probing their genetics, development, and evolutionary relationships. Along the way he has explored macronuclear assortment and presented a model of subnuclear segregation, developed techniques and models for understanding the transmission of corticotypes, and used isozyme data and selected nucleotide sequences to determine phylogenetic relationships and the evolution of the tetrahymenids in relation to other ciliates and other organisms. Many of his ideas and concepts derived from his work are expressed in his book enti-

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tled *Experimental Ciliatology,* which he originally wanted to title *Sex and the Single Cell.* In addition, he has had a life-long interest in the sociology, philosophy, and development of science.

One of David Nanney's most quoted early observations is found in his 1953 paper in *Biological Bulletin,* "Nucleo-cytoplasmic interaction during conjugation in *Tetrahymena.*" After describing the sequence of normal stages of conjugation, centrifugation was used to displace nuclei from their normal cytoplasmic site. From the abnormalities observed, he concluded that different locations in the cytoplasm had different fate-determining activities with regard to nuclear differentiation, and that experimental alteration in the position of nuclei resulted in alterations in nuclear fate that are the essence of the nuclear dimorphism found in ciliates. These data have been particularly influential on various investigators, particularly those in France and Japan currently studying the triggers for nuclear differentiation in *Paramecium.*

Nucleocytoplasmic circuitry was an early theme of Nanney's work, starting with his research on mating type determination, first in *P. tetraurelia* and continuing with *T. thermophila.* Elegant "visual" models were designed to capture the interrelationships between systems of karyonidal and cytoplasmic inheritance in *Paramecium* to determine where the "homeostat" controlling a nuclear state was located. The concept of "nuclear states" was extended to the system of karyonidal inheritance seen in *T. thermophila.* A progressive restriction of mating type potentialities was envisioned, based on the selection of fewer competitive biochemical pathways. The original interpretation of the selfer data was that selfers are an intermediate developmental stage, having an "unstable" nuclear state in which the competition between two biochemical pathways is unresolved. The implications of the rates of "assortment" of pure mating types from selfers for a "particulate" model based on "macronuclear subunits" was appreciated when Schensted's computer simulations showed agreement with the experimental assorted numbers. This led to the hypothesis of the compound genetic nature of the macronucleus, first proposed by Sonneborn for *Paramecium,* and now elaborated in the context of *T. thermophila* mating type differentiation (Allen and Nanney, 1958: "An analysis of nuclear differentiation in the selfers of *Tetrahymena*"). This opened up a subdiscipline of its own, namely, the fundamental genetic behavior of the subunits comprising the macronucleus. Later Dave reanalyzed his mating type data in collaboration with Steve Portnoy. Having to peer review one of these papers caused Ed Orias to immerse himself in the mating type data and provided the immediate stimulus for his own later model of mating type determination, proposing DNA rearrangements during the postzygotic development of a new macronucleus.

We were there in the early years at the University of Michigan, Ed as one of Dave's first graduate students and Sally as a "postdoc" (an unemployed spouse and nepotism victim). The atmosphere in the lab was friendly, fun, and above all philosophically challenging. Accompanied by their respective spouses, Dave and Sally toured the upper part of Michigan, spending a memorable smoke-filled night in a cabin in Wilderness State Park. David collected water samples, including a sample from a drainage ditch beside the road somewhere in Alpena, Michigan. (Later this yielded a strain of *T. thermophila* dubbed ALP-1, one of the progenitors of inbred strain D). Some of the Alpena collection contained "variety 8" (later named *T. pigmentosa*), which served as material for Ed's doctoral thesis on mating type determination in that species. Sally became involved in the famous "selfer" project, which Dave dubbed "Frankenstein" since her naive experimental design required 1,200 single cell isolations each day, using the old fashioned three-well depression slides (or 1,200 slides in 30 vegetable crispers). This led to the 1958 Allen-Nanney paper complemented by Irene Schensted's computer simulations using MIDAC (Michigan Digital Automatic Computer, a prehistoric mainframe computer housed in a hangar at Willow Run airport). These studies also led to Sally's abandonment of the histocompatibility locus-2 and mouse genetics, turning down an awarded NIH grant and moving on to protozoan genetics. When Dave left Michigan in 1959, Sally inherited Dave's space.

Ed acknowledges Dave Nanney's profound influence on his life, in several fundamental aspects that include, but are not limited to, Dave's crucial contributions to his formation as a scientist. For example, Ed met his future wife, the former Judy Dodge, in a recitation section of Dave's General Genetics course. Later, Dave and Jean Nanney stood in place of Ed's parents at their wedding. Dave and Jean treated students as members of their family. Among take-home lessons from Dave that made a lasting impression, Ed remembers such statements as "A question well asked is a question half answered," or "Ideas are cheap; the limiting step is the data." Or, in response to a request for advice on a job offer from the University of California at Santa Barbara: "It's your decision; you are the one that will live with its consequences."

Coinciding with a sabbatical at the California Institute of Technology in Ray Owen's lab, Dave became interested in the immobilization antigens of *Tetrahymena.* Collaborating first with Jean-Marie Dubert, he turned his attention specifically to the genetics and developmental aspects of the expression of what is now known as the *SerH* locus. He continued working with the *SerH* locus when he moved to the University of Illinois. Dave's students followed up, studying the genetics and expression of serotypes T (Ruth Brosi Phillips), L (Betty Juergensmeyer), and S (Frank Grass). Peter Bruns extracted the H antigen as his doctoral thesis. Paul Doerder isolated and characterized muta-

tions that regulate *ser* gene expression, and has continued to work on the genetics and biochemical characterization of the *Ser* loci. In collaboration with Dick Hallberg and Gary Bannon, a cDNA clone isolated by Duane Martindale was shown to contain a segment of the *SerH* gene and was later characterized in terms of its transcriptional and translational control. To this day Paul remains the chief "collector" among Dave's students, having isolated from nature a number of new strains which contain new *SerH* alleles and new *Ser* loci.

Examination of *SerH* heterozygotes quickly led to Nanney's discovery of allelic exclusion and of the general significance of macronuclear assortment in the *Tetrahymena* macronucleus. Moreover, the kinetics of assortment at the *Ser* locus were similar to that of the selfers and predicted the same number of assorting units. Differences were observed in the proportion of units expressing one or the other allele depending on which two of the four alleles were present in the heterozygote. He proposed that the assorting units were diploid subnuclei and that the macronucleus was a compound nucleus containing 45 diploid subnuclei. The implications of his hypothesis for macronuclear structure, differentiation and replication were elaborated clearly in a landmark publication in 1964 entitled "Macronuclear differentiation and subnuclear assortment in ciliates." Although a combination of later genetic and molecular work led to the idea that the assorting subunits are haploid, this paper provided a remarkably lucid view of the genetic events associated with the developing and the mature macronucleus. It also provided an intellectual framework for subsequent work by Sally Allen, Peter Bruns, Paul Doerder, Ed Orias, and their students. These genetic studies gave access to events occurring in individual macronuclei. They complement the elegant molecular approaches now being used to study the developing macronuclei, since molecular approaches generally have been based on the average properties of many developing macronuclei. Indeed, the rigorous and imaginative interpretation of genetic experiments started by Dave Nanney and carried out by him or his students over the past 30 years have provided the cornerstone for much of our current knowledge of the developing macronucleus.

According to Paul Doerder, as a Ph.D. mentor Dave Nanney was more of an advisor than a director. "He was always available, always willing to help, but rarely, if ever, domineering. He allowed the student to work at his/her own pace, and there never was pressure to obtain results for the next paper or grant application. Lab meetings consisted of critical analysis of recent papers, discussion of recent results in the lab, dissection of the latest Nanney manuscript, or (and we looked forward to these) a spontaneous lecture of the history of some problem in ciliate genetics, usually replete with lore about Tracy Sonneborn." Having worked as a postdoc in Dave's lab, Lea Bleyman observes that "Dave is a person who loves family and he understood that one's personal life is as important as one's professional life." Indeed, dinners at the Indiana Street house or picnics at the Embarras River farm (wilderness) always included family; visits or phone calls to Dave and Jean always included exchange of news of spouses, children, grandchildren, and friends.

Dave Nanney pioneered the analysis of cortical pattern in *Tetrahymena* starting in the 1960s and continuing into the 1970s. Even though this work involved relatively few (but crucial) genetic crosses and no molecular analysis, the approach was thoroughly that of a geneticist. Dave started the project by analyzing cortical configurations in *Tetrahymena* clones that had been maintained under standard stock conditions of monthly transfer followed by growth of subclones in fresh medium for approximately 20 fissions. This method was superb for studying both variation and its inheritance. Stocks maintained under conditions of monthly transfer generated far more intraclonal variation than did stocks maintained under continuous growth, and the subcloning of these stocks allowed for evaluation of inheritance of this intraclonal variation.

Using these methods, Dave made several major discoveries. Perhaps the best known demonstrated the complementary principles of cortical inheritance and ultimate genic control as applied to the number of ciliary rows (the "corticotype"; Nanney, 1966: "Corticotypes in *Tetrahymena pyriformis*"). Cortical inheritance was demonstrated by the maintenance of corticotypic differences in subclones for a number of generations greater than that required for the dilution of non-replicating molecules. Ultimate genic control was suggested by the drift of the corticotype to a "stability center" at a rate inversely proportional to the initial distance from that center (Nanney, 1966: "Corticotypic transmission in *Tetrahymena*").

Even more impressive were the discoveries relating to cortical integration. Whereas other investigators had made inventories of variation in cortical parameters, Dave paid attention to the coordinated variation of different aspects of cortical geometry. What remains constant when many features are varying simultaneously? By asking this question, Dave made the signal discovery that the relative circumferential position of the contractile vacuole pores remains nearly constant as the number of ciliary rows changes. This led to the general conclusion, expressed in characteristic Nanney fashion, that "The concepts of fields and gradients so widely employed in a description of organismic integration in multicellular forms are equally as applicable (and equally as sterile perhaps) in a consideration of organization at the cellular level" (Nanney, 1966: "Cortical integration in *Tetrahymena*: An exercise in cytogeometry").

These two discoveries do not exhaust the list of major findings made by using simple approaches. Two others

serve as excellent examples of Dave's method of studying both cortical variation and the constancy that lurks behind this variation. With regard to variation, he discovered strains that exhibited "cortical slippage", in which oral primordia appeared next to ciliary rows other than the usual right postoral ciliary row. He quickly realized that this meant that any ciliary row can potentially serve as the site of origin of an oral primordium and hence, even if there were basal body DNA, there could be no relevant genic diversification of different ciliary rows (Nanney, 1967: "Cortical slippage in *Tetrahymena*"). With regard to constancy, although he found that in normal *Tetrahymena* cells, the total number of ciliary rows varied, this number was subject to regulation, once again proving the existence of global integration in the ciliate cortex (Nanney, 1971: "The constancy of cortical units in *Tetrahymena* with varying numbers of ciliary rows").

To make the inventory of Dave Nanney's major discoveries concerning the cortex more complete, we would need to describe his observations on inheritance and integration of homopolar doublets as well as his comparative studies across species. Even the partial description given here shows clearly how much he achieved by technically simple observation coupled with clever quantitative analysis. He himself has reviewed much of this work in a clear and eloquent manner (Nanney, 1968: "Cortical patterns in cellular morphogenesis"; Nanney, 1972: "Cytogeometric integration in the ciliate cortex").

The person most influenced by Dave Nanney's research on the cortex is possibly Joe Frankel, although others could be mentioned: Paula Cho, Janina Kaczanowska, Andrzej Kaczanowski, and Linda Hufnagel, to name a few. Hufnagel commented that Dave's "thorough analytical approach to ciliate morphogenesis had a profound influence on her own approach to the subject". She has found it a challenge to incorporate Dave's findings and conclusions regarding morphogenesis in *Tetrahymena* into her own model for morphogenesis in ciliates. She also commented that she "expects to be reading and rereading Dave's papers for the rest of my life." Joe Frankel said he was stimulated and inspired by discussions with Dave in 1965 when Dave visited the University of Iowa and in 1966 at the ciliate genetics meeting at Shelter Island. Frankel started his work on spatial patterning in *Tetrahymena* in the Fall of 1972. He considers his own accomplishments in this area to be a continuation of the research program that Dave Nanney began. In his synthetic article in this issue ("Genes and Structural Patterns in Ciliates" Vance Tartar and the "Ciliate Architects") Joe explores the connections between Tartar, Sonneborn, Beisson, Nanney and himself.

Curiosity about *Tetrahymena ménages-a-trois* led to an efficient way to generate cells with haploid micronuclei, and to an investigation of copy number regulation in haploid and aneuploid macronuclei. It turned out that in asymmetrically conjugating triplets, the "cell in the middle" receives migratory gametic pronuclei from both its mates and becomes triploid. However, it can only donate its migratory pronucleus to one mate; the third mate becomes haploid. This discovery led to the isolation of nullisomic *Tetrahymena* in Peter Bruns' lab, a unique and powerful mapping tool made possible only by the nuclear dimorphism of the ciliates. This series of investigations in Nanney's lab was done in collaboration with Rosa Maria Preparata and Hans-Martin Seyfert, and culminated in an insightful review in 1979, "Genetic evidence concerning the structure of *Tetrahymena thermophila* macronucleus."

In the early 1970's Nanney got "into" isozymes with his student Dennis Borden, Elizabeth Miller, and his isozymer colleague Greg Whitt. This work was later continued with his long-term collaborators Ellen Simon and Barbara Meyer. This work built upon the earlier work of Sally Allen on the genetics of the esterases and acid phosphatases in *T. thermophila* and her very modest comparisons between a few of the species in the *T. pyriformis* complex. By this time Nanney had amassed a considerable collection of strains representing many species of *Tetrahymena*. The electrophoretic pattern of various isozyme systems was compared between species and strains. The data could be used in two ways: as a diagnostic tool to identify species and to construct phylogenetic trees. Several amicronucleate strains of *Tetrahymena* had lost their true identity in the course of their travels from lab to lab. These were correctly sorted out using isozyme patterns in a paper with the original title: "Will the real *Tetrahymena pyriformis GL* please stand up." that was published in Science in 1973 under the less dazzling title "Isozymic heterogeneity in *Tetrahymena* strains". Toru Higashinakagawa was able to sort out whether variation in the rDNA transcription initiation site was real or spurious as a result of Nanney's proper reclassification of strains and species by isozyme pattern. Clifford Brunk also benefitted in his work from the availability of the species collections and said: "Thanks to the Nanney lab we have a set of well-characterized species that can be easily manipulated. The *Tetrahymena* species are an excellent source for examination of molecular evolution, ranking with the *Drosophila* complexes." Critical to these studies, and to subsequent investigations of *Tetrahymena* genetics and evolution, was the development of methods of liquid nitrogen preservation of *Tetrahymena* cells by Ellen Simon in Nanney's lab.

An evolutionary thrust that began with corticotypes now bubbled forth with isozyme data and later with nucleotide comparisons of various RNA gene sequences, and remains an area of active work by Dave Nanney. A conflict in measuring genetic distances within the tetrahymenine ciliates became apparent when it was seen that the morphological data suggested closer relationships between species than did the molecular data. The rate of evolution appeared to

be much faster for the molecules than for structures. In a witty article published in BioScience in 1982 ("Genes and phenes in *Tetrahymena*") Nanney concluded that molecular evolution is to a large extent uncoupled from morphological evolution in the ciliates; that is, genes and proteins continue to accumulate differences while the overall morphology of the cell and its organelles remain constrained in what is apparently a successful evolutionary strategy. These ideas have particularly influenced André Adoutte who found that this observation "remains one of the nicest demonstrations of neutral evolution and is the best available explanation for the paradox of the huge genetic differences separating sibling species in protists".

The evolutionary studies have included Craig Van Bell's postdoctoral work and have influenced Dennis Nyberg and Nicola Ricci, who are interested in the ecology as well as the evolution of ciliates. More recently Dave stimulated the development of Franco Preparata's "Phylogen" program and has applied "string analysis" to the early evolution of the eukaryotes.

Dave's passion for collecting new species of *Tetrahymena* continues to this day. Janina Kaczanowska recalls Dave's visit to Poland in 1984 and a sight-seeing trip to the area of the Mazurian lakes. "We stopped casually for awhile near a bridge. Dr. Nanney then took a vial from his pocket and quickly collected a sample of murky water and said dreamily that if there was a new species of *Tetrahymena* in the sample that he would name it *Tetrahymena mazurka.*" Today there may be a *Tetrahymena mazurka,* although Janina is not sure if it was isolated from that particular water sample.

There is one more important area to which Dave Nanney has made a contribution: the sociology, philosophy and development of science. In recent years he has been particularly concerned with serious problems: the problems of "little science" (basic research) in a scientific world dominated by "big science," applied science, and biotechnology; the stresses placed upon science and scientists as support for science inexorably reaches a plateau; the graduation of doctoral students who are technically "trained" in a very narrow sphere rather than thinkers who can grapple with global problems; finding a way to provide creative scientists with the means and the funding necessary to pursue their serious work, however unfashionable it may be, and indeed treasuring their unorthodoxy. By example, Dave has taught us to live up to our duties and responsibilities as informed citizens of the world of science. Dave and Jean together set high ethical standards for relating to members of Dave's research group, standards that we have strived to perpetuate.

With the current preoccupation of the press and Congress over scientific fraud, Paul Doerder is reminded of what Dave has often said in the context of persuading *Tetrahymena* to reveal its secrets: the truth is much more interesting than anything one can make up. This characterizes Dave's approach to science. With this truth in mind, and in the name of all who, in their own way, contributed to this volume, we dedicate this special issue of *Developmental Genetics* to David Ledbetter Nanney.

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Work Not Co-Authored, but Done at Least in Part in His Lab and Supported at Least in Part by His Grant

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