BEGINNINGS AND BRIEF SYNOPSIS

I was born in Palermo on April 30, 1919, an only child to a mother deeply involved in literature and literary activities and a father devoted to ranching, vine growing, and wine making. My high school education had a literary and classical orientation, and my ambition was to enter the study of medicine. I graduated in 1942 summa cum laude from the University of Palermo Medical School with a thesis in pediatrics and spent my postgraduate years and time as assistant professor of pediatrics (1942–1962) at the Children's Hospital in Palermo, attaining the rank of libero docente (university lecturer) in 1948.

In November 1962, I became chair of pediatrics at the University of Perugia and directed its pediatric clinic until January 1966. Since then I became chair of pediatrics at the University of Pavia until October 1989. After attaining emeritus status, I remained a professor of pediatrics in Pavia. Over 27 years of teaching, I was privileged to train many students, 5 of whom are now chairs of pediatrics in Pavia, Perugia, and Varese and 10 of whom became directors of pediatrics or pediatricians in chief in major hospitals. My major fields of interest and research were immunology and immunobiology.

THE PALERMO YEARS

This opportunity to recollect and recount some aspects of my professional life as a pediatrician allows me to focus on the several research areas of importance to me during my early years. In retrospect, it seems evident to me that in part my interests were focused and enthusiasm committed to the needs of the time and place, at a time when it was the normal expectation for a young faculty member to have and develop competence and expertise in several fields at once.

As I have spent my first 43 years (up to 1962) in Palermo, Sicily, where extreme poverty was widespread as recently as the 1950s, I first chose to address some urgent aspects of nutrition, including the pathophysiology of infant megaloblastic anemia (Gerbasi anemia) that was common in breast-fed infants of very poor mothers. I was able to demonstrate that this condition was due to a nutritional deficit of vitamin B12 [Burgio, 1954; Burgio and Russo, 1956] and also that nodular purpura of the infant [Burgio, 1957] was caused by vitamin K malabsorption. In addition, I was forced to deal with Kwashiorkor [Burgio, 1961, 1967] and the immunological aspects of typhoid fever [Burgio and Bavastrelli, 1954], brucellosis [Burgio, 1955], toxoplasmosis, and leishmaniosis [D'Alessandro and Burgio, 1954].

These early studies almost forced one to recognize that the response to these environmental stimuli and infectious agents had an essentially genetic basis; thus, immunogenetics then (in 1963) became my main research interest and focus for the rest of my career.

In 1976, the Italian Pediatric Society asked me to prepare an introduction to a paper on primary immunodeficiencies for its national congress. My characterization of "life as an immune phenomenon" [Burgio et al., 1976a] led to the insight that many immunodeficiencies represented "inborn errors of immunity" [Burgio and Ugazio, 1985], in the same way in which we have been speaking of inborn errors of metabolism from Garrod (1908) onward. This view allows an analogously simple insight into and characterization of the two great biological systems on which our life (and that of all animals) depends for survival. However, in addition to the general analogous aspects of these two systems shared by all animals, it is obvious that in a manner analogous to Garrod's concept of biochemical individuality there also is such a thing as immunological individuality, or the individual way of reacting, unique to each human being and genetically based.

IMMUNOLOGAL INDIVIDUALITY

The concept of immunological individuality, powerfully aided and reinforced by the discovery of the HLA system, has been a major theme in my work for over a decade [Burgio, 1984]. Reflecting on Garrod (1931) on one hand and Burnet (1949) on the other, it was easy to view the biological behavior of individual human beings (essentially, the self) when facing the alien (essentially, the nonself) in terms that were increasingly molecular.
from an analytical perspective [Burgio, 1986, 1990, 1994a]. By combining my interests in immune behavior and genetic background, I focused on syndromes whose natural history suggests the existence of genetic immune dysfunction. Accordingly, I began work on Down syndrome, to which I have devoted myself continuously for some 30 years [Burgio and Severi, 1965; Burgio et al., 1981]. However, no pediatrician enchanted by immunology as a most instructive approach to understanding how a new being deals with the old environment was so inspired as to regard the small infant as a subject of study [Maccario and Burgio, 1987; Burgio et al., 1990].

Clinically intriguing issues such as IgA deficit [Burgio et al., 1980a; Plebani et al., 1986], bone marrow transplantation [Burgio et al., 1988c], or the molecular basis of predisposition to certain diseases [Burgio et al., 1993; Burgio, 1994] nevertheless all entail strong genetic and immune premises. It is these shared premises that exerted a particular attraction to me. I will return to these issues after an excursion into some syndromological encounters [Burgio and Biscatti, 1965; Burgio et al., 1974a; Wiedemann et al., 1983; Burgio et al., 1988a].

IN A MODEST SYNDROMOLOGICAL VEIN

In Palermo [Burgio, 1962] and then in Perugia [Burgio, 1962; Burgio and Severi, 1965] and Pavia [Burgio, 1968; Lo Curto et al., 1974; Burgio and Fraccaro, 1974], I have been involved, for clinical and didactic reasons, in disorders of sex differentiation. I had studied a short, 14-year-old girl with a webbed neck, cubitus valgus, pulmonary stenosis, a reduced number of ovarian follicles and 46,XX chromosome constitution [Burgio and Biscatti, 1965]. An international congress on disorders of sex differentiation, which I organized in Perugia in 1964 with F. Severi [Burgio and Severi, 1965], gave me an opportunity to report on this observation in the presence of such authorities as J. R. Bierich (Hamburg), P. H. Carpentier (Antwerp), W. M. Davidson (London), J. M. Edwards (Birmingham), M. Fraccaro (Pavia), L. Gedda (Rome), G. A. Hauser (Lucerne), R. Jean (Montpellier), M. Jeune (Lyon), E. Joss (Bern), M. Lamy (Paris), W. Lenz (Hamburg), L. Overzier (Mainz), A. Prader (Zürich), P. Rosa (Bruxelles), R. Turpin (Paris), H. Weicker (Bonn), K. Zuppinger (Berne), and R. Zurbrügg (Berne).

A year after that memorable meeting I came across the efforts of Opitz et al. [1980], emphasizing the Noonan syndrome in girls, a genocopy of the Ullrich-Turner syndrome. Dr. Opitz worked in Iowa City at a time when N. Jacqueline A. Noonan and her pediatric cardiology co-worker, Dorothy Emke, were conducting their pioneering studies on this entity. I have not forgotten the case of this girl who became for me a case of Noonan syndrome before its time, especially since meeting her again, 20 years later, married and the mother of two apparently healthy children.

Gonosomal aneuploidy became a topic of interest with the study of two exceptionally interesting patients. The first was a 12-year-old boy mosaic for three cell lines (46,XY, 46,XX, and 47,XXX) with mixed gonadal dysgenesis [Burgio et al., 1966a]. The other was a 7-month-old boy with descended testes and normal genitalia, and extreme growth retardation (weight, 3,800 g; length, 56.5 cm) whose chromosome constitution was 45,X in blood, skin, and cells cultured from testis [Lo Curto et al., 1974].

Because of their prevalence, it was difficult to set aside an ongoing interest in these disorders, further stimulated by the distinguished pioneer cytogeneticist Marco Fraccaro of Pavia, with whom I worked frequently and organized, 10 years after the Perugia meeting, a congress in Levico (Italy) on Genetic and Endocrine Disorders of Sex Development [Burgio and Fraccaro, 1974]. Participants included F. Ballesta (Barcelona), J. R. Bierich (Tübingen), E. Bühler (Basel), P. Canlorbe (Paris), B. Dutrillaux (Paris), C. E. Ford (Oxford), D. Knorr (München), J. Lindsten (Stockholm), M. F. Lyon (Harwell), U. Mittwoch (London), R. A. Pfeiffer (Lübeck), A. Prader (Zürich), M. Tolksdorf (Kiel), H. Wallis (Hamburg), M. Zachmann (Zürich), and R. Zurbrügg (Basel).

A few years later, I noted severe dwarfism in two sisters with a skeletal dysplasia that evolved, albeit only partially, into something that resembled diastrophic dysplasia but with a cartilage histology distinctly different from that typical of the latter entity. I described the condition as pseudodiastrophic dysplasia [Burgio et al., 1974a; Eteson et al., 1986; Cetta et al., 1987].

Finally, I must note two other unusual conditions. The first is the Proteus syndrome, to which, from a histological and biochemical perspective, I contributed with authentic passion [Wiedemann et al., 1983; Burgio and Wiedemann, 1984]. The other is a three and 3/12-year-old girl with asymmetrical Marfan syndrome expressed only on the left side of her body, with dislocated lens of the left eye and prolapse of the mitral valve [Burgio et al., 1988a]. The histochemical study on skin from both sides of the body contributed substantially to the verification and interpretation of this exceptional case [Godfrey et al., 1990].

Finally, I reexamined the causal and pathogenetic relationship of skeletal and hematopoietic involvement in the bone marrow dysostoses, dedicating this work [Burgio et al., 1987a] to the memory of Conrad Gasser of Zürich, who had died 5 years earlier and who had talked with me more than once about his interest in this matter.

It would have been easy for me to continue working on syndromes; however, after having been attracted to the great theme of the way of reacting, I moved on to the study of the immune system in Down syndrome.

While there are diseases caused by immunodeficiency on a genetic basis (such as primary immunodeficiencies), there are also other well-known ones that are also genetic or chromosomal and whose course characteristically includes immunodeficiency [Burgio and Ugazio, 1982]. The most recent classification of immunodeficiencies of the World Health Organization (WHO) (Clinical and Experimental Immunology 99,
Supplement 1, January 1995, 2–24) clearly shows that such a clinical approach to classification is appropriate. Particularly after Mellon (1963), I too had noted that antithyroid antibodies often appear in children with Down syndrome [Burgio and Severi, 1965/1966]. This was another reason why I thought it worthwhile to investigate their immune systems.

DOWN SYNDROME AND THE IMMUNE SYSTEM

It is widely acknowledged that Down syndrome is not simply a morphological condition that includes intellectual deficit but is a syndrome that can be interpreted, much more broadly, as the model of a unique and particularly well-characterized biological and biofunctional entity. Starting from this premise, which increasingly acquired important contributions from several disciplines in the 1970s, I organized, again with M. Fraccaro (Pavia) but also with L. Tiepolo (Pavia) and U. Wolf Freiburg, a congress on Trisomy 21 (Santa Margherita Ligure, Italy, 1979). Among the participants were G. Annerén (Stockholm), K. Ber- glund (Stockholm), A. Boué (Paris), J. Boué (Paris), D. R. Cox (San Francisco), L. B. Epstein (San Francisco), C. E. Ford (Abingdon), N. Fresco (Paris), A. Gath (Suffolk), L. Iselius (Stockholm), B. Kjessler (Stockholm), J. Lejeune (Paris), J. Lindsten (Stockholm), L. Marsk (Stockholm), D. M. Kompx (New Haven), S. M. Caniglia (Paris), R. Eife (München), B. E. Favara (Halifax), A. Fischer (Paris), J. G. Goldberg (Buenos Aires), C. Griscelli (Paris), M. L. Hansmann (Kiel), K. Hinkeldey (Hamburg), H. Holtmann (München), S. E. Janka (Hamburg), D. M. Komp (New Haven), S. Ladisch (Los Angeles), J. McNamara (New Haven), and C. Nezelof (Paris). This symposium led to the creation of a registry of cases of this syndrome (the International Registry for Hemophagocytic Lymphohistiocytosis), which has been based in Pavia since December 1988.

IMMUNOLOGICAL STUDIES OF INFANCY

If there is a biological or organ system whose ontogeny is most typically stimulated by environmental factors, it is the immune system. Functional maturation is accompanied and caused by cell differentiation and humoral competency. The immunological characterization of the newborn infant, particularly from an ontogenetic perspective, has been one of the most productive areas of my group of co-workers over the years, several contributions having been made by myself [Burgio et al., 1976b, 1987b, 1990]. I would like to mention in particular the study of skin reactivity to phytohemagglutinin and to some microbial antigens [Burgio, 1964; Burgio et al., 1964, 1968, 1969, 1970, 1971, 1977]. Together with L. A. Hanson (Göteborg) and A. G. Ugazio (Pavia), I also devoted an international meeting [Maccario and Burgio, 1987] to the immunology of the neonate. Participants included F. Aiuti (Rome), U. Andersson (Stockholm), J. A. Bellanti (Washington), J. L. Butler (Birmingham), F. S. Cole (Boston), R. A. Good (St. Petersburg), R. N. Hamburger (San Diego), A. Hayward (Denver), H. R. Hill (Salt Lake City), F. Laurenti (Rome), R. Macario (Pavia), A. Mantovani (Milan), D. L. Nelson (Bethesda), O. Stutman (New York), J. L. Touraine (Lyon), and J. L. Virelizier (Paris). More recently, I have devoted some interest to the behavior of IgG subclasses with an ontogenetic criterion [Plebani et al., 1989].

IGA DEFICIT

The prevalence of this deficit in the population is comparable to that of Down syndrome. However, that is not the only reason why I included it in my research program. The IgA class of immunoglobulins, specifically secretory IgA (IgAs), is the first line of defense in a person in contact with an environmental antigenic stimulus and is a special impetus to those interested in the individual way of reacting. Having studied the ontogeny of IgAs [Burgio et al., 1980b] it was obvious to investigate partial deficits of these factors [Burgio et al., 1980a; Plebani et al., 1986] without neglecting the possible links between IgA deficits and the HLA
antigens [Cuccia-Belvedere et al., 1989]. This is a twice genetic relationship, since a primary IgA deficit, so important in disease predisposition, is as genetic as the basis for the production of the unique and complex set of HLA molecules of each individual, which, in turn, are of relevance in predisposing to the development of some diseases.

**BONE MARROW TRANSPLANTATION**

*(INTERPRETED AS A LESSON IN BIOLOGICAL INDIVIDUALITY)*

From a pediatric viewpoint, one of the high points in the history of bone marrow transplantation is constituted by the first two transplants in 1968, to which I dedicated a couple of papers [Burgio et al., 1988c; Burgio and Nespoli, 1992]. However, the most significant genetic aspect, which has deep bioethical consequences in pediatrics itself, as well as organizational implications, is still the question of finding the compatible donor. Such a donor is, ideally, a brother or sister of the sick child [Burgio et al., 1989, 1994a]. This is a problem whose solution, in childhood, can be expanded to the point where the sick child’s parents procreate a new child in the expectation of providing a compatible donor sibling for their sick child. My experience in Pavia in this regard probably was the first to be reported: “Programming of Bone Marrow Donor” [Burgio et al., 1987c; 1988b; Burgio and Nespoli, 1992]. This concept will probably remain an ethical controversy for a long time: “Conceiving a Child to Save a Child” or “The Child Conceived to Give Life” [Burgio et al., 1994a,b, 1997a].

All of the problems of bone marrow transplantation, with its severe risk of rejection or of graft-versus-host disease (GVHD), have become paradigmatic in a model of self-nonselves and, at the same time, a lesson in immunology and genetics [Burgio, 1990]. The molecules of the HLA system conspicuously and materially provide the script for this lesson, which has also been intensely debated in the printed and spoken media because of its news value and its human drama overtones. Very often the problem of searching for donors and establishing special banks touch the awareness of the public at large and affect the individual and collective conscience. Few subjects, more than transplants, are in fact able to evoke at the same time genetic immunologic and bioethical themes. With respect to bone marrow transplantation, I have suggested that it was appropriate to recommend an alternative: I wonder whether nowadays it is still sufficient to speak and act according to the centuries-old principle of primum non nocere (first of all, do no harm), or whether it would instead be more appropriate, more in tune with medical progress, and more supportive of human solidarity to propose an ethic of primum adiuvare (first of all, help) [Burgio, 1994a].

Quite aside from the bioethical problems raised by transplants in children, I organized, together with J. D. Lantos (Chicago), a symposium in pediatric bioethics devoted to primum non nocere today [Burgio, 1994b]. Participants included, among others, A. Boué (Paris), P. Cattorini (Florence), G. Corbellini (Rome), D.V. Engelhardt (Lübeck), R. Gillon (London), M. Mori (Milan), M. Siegler (Chicago), A. G. Ugazio (Brescia), and C. Versluys (Utrecht).

**THE BIOLOGICAL EGO**

Starting from knowledge regarding transplantation and especially bone marrow transplantation (with which I am most closely involved), I believe that the step toward the identification of man as a biological ego is a short one. Indeed, owing to what *Homo sapiens sapiens* of the end of the 20th century have learned about transplant(s), they have become aware of their immune genetic-molecular individuality; in other words, humans have become aware of the uniqueness of the individual immune self. This awareness has now become widespread [Burgio, 1984, 1985; Burgio and Nespoli, 1989; Burgio, 1990a, b, 1991b; Burgio and Nespoli, 1992].

**MOLECULES AND PREDISPOSITIONS**

The concept of molecular substrates to predispositions is very rich in biological implications: from the ease (or lack thereof) in contracting diseases to the interpretation of low responders to vaccines. Ethnic and biological implications also affect this view, e.g., highlighting different HLA antigen involvement in different ethnic groups affecting predisposition to illness or to failure to respond to vaccines. There is an enormous body of literature on the subject of HLA antigens in relation to the diseases that are associated with them. Predispositions to diseases have evolved from the vague, centuries-old concept of diathesis introduced by Galen (129–199 A.D.) to being acknowledged as a genetically rooted fact, indeed, an HLA-allelic fact, to a large extent. This has significantly enriched the chapter on predispositions with new knowledge [Burgio, 1993, 1994a].

Diathesis and predisposition are two terms for a concept that is experiencing rapid change [Burgio, 1995a]. Its progress has become more and more analytically genetic and molecular: today, we have considerable knowledge of the genetics of predisposition to atopy, which, some time ago, I referred to as a minimal immunodeficiency [Burgio et al., 1978b]. Often, more severely than in atopy, pathogenetic activities of the immune system are expressed as autoimmune disease whose study has repeatedly spurred my interest [Burgio et al., 1966b; Burgio and Vaccaro, 1969; Burgio and Vaccaro, 1970, 1972; Burgio and Ugazio, 1975, 1976; Martini et al., 1986a, 1986b, 1987; Aricó and Burgio, 1989; Burgio and Martini, 1990; Martini et al., 1990; De Benedetti et al., 1991; Ravelli et al., 1994].

If there is a long history behind the subjects that I have considered, it most certainly is the one on predispositions, which began with Galen’s diathesis. It is also important for how concepts evolve in medicine [Burgio, 1993, 1994a, 1995a]: an evolution that enriched medical culture and monitors the steps of this progress.
A FEW NOTIONS OF HISTORY AND A FEW BOOKS

Monitoring progress means monitoring history. Being sensitive to the principle that medicine (or science) without a history is like a man without memory, I have dwelled on some retrospective evaluations of the fetal thalidomide syndrome [Burgio, 1981], the origin of the concept of atopy [Burgio, 1982], the DiGeorge anomaly [Burgio and Ugazio, 1985], the evolution of concepts regarding some immunodeficiencies [Burgio et al., 1991; Burgio and Ugazio, 1992; especially X-linked agammaglobulinemia, Burgio et al., 1993], the history of transplants [Burgio and Nespoli, 1992], and the Wiskott-Aldrich syndrome [Burgio, 1995c], not to mention the centuries-old theme of predispositions, since the days of diathesis [Burgio, 1995a].

I have followed the evolution, in the course of time, of adolescent care on the part of pediatricians [Burgio and Lorini, 1975; Burgio and Ottolenghi, 1994; Burgio, 1995b]; this is one of the most significant subjects for the pediatric management of social health, which is surfacing particularly in North American literature. Finally, I thought that I could make a contribution to the diffusion of medical knowledge not only by honoring its history but also by addressing issues of wide sociopediatric, sociopedagogic, and didactic interest (with the ultimate goal of training better pediatricians) [Burgio and Lorini, 1975; Burgio, 1990a, b, 1991a; Burgio and Scotta, 1991] and by writing a few books.

It’s a short stride from the pleasure one finds in history to the pleasure induced by the diffusion of culture. In my 27 years of teaching e cathedra I have enjoyed a particularly productive didactic relationship with students through their curriculum and later with postgraduates. I have taken part in countless congresses, including international pediatric ones, where I gave official reports (as in Mexico City, 1968; Vienna, 1971; and Buenos Aires, 1974). I have written several books for Italian publishers and wish to dwell briefly on one of them: a book of approximately 1,000 pages, now into its fourth edition, in which I presented, through problems and clinical summaries, pediatrics as I believe physicians should know it. That is why I entitled it Pediatria Essenziale (Essential Pediatrics) [Burgio et al., 1997b]. It has had enormous success (first edition, 1978).

I will not mention any of my contributions to many pediatric books published in Italy, but I think I should mention my immunologically oriented contributions to “Pediatric Therapy” [Rosen and Burgio, 1993; Lepow and Burgio, 1993; Kobayashi et al., 1993]. In fact, this collaboration with the prominent American pediatric immunologists R. H. Kobayashi (Los Angeles), L. Lepow (Albany), F. S. Rosen (Boston), and R. E. Stiehm (Los Angeles) was highly rewarding for me. I believe that a nuanced emphasis on culture is among the chief duties of researchers and teachers and for me has been a source of true pleasure. And of course, no experience could be more intensely desired and hoped for than one that transforms duty into a pleasure.

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