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Progress in pathology

Contributions of pediatrics and pediatric pathology to the body of knowledge regarding human disease

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Summary A century or so ago, pediatrics and pediatric pathology did not exist. Then, many fetuses/newborns died in utero or shortly after birth. With time, the issue of sepsis was addressed, and a greater number of newborns survived. Gradually, in this soil, the disciplines of pediatrics and pediatric nursing arose, as some recognized that infants were not merely small adults but were, in fact, quite different. Years later, pediatric pathology developed as a field of exploration. Today, pediatric pathology is a specialty, as witnessed by training programs, societies devoted to research and education, an expanding number of textbooks and innovative research. Pediatric pathology is distinct from adult pathology, as seen by the diversity of malformations and metabolic diseases stemming from mutations, the immaturity of the newborn’s immune system, and the types of neoplasms germane to infants and children. Much of the progress in these areas was facilitated by the simultaneous emergence of cytogenetics and molecular biology and their powerful tools of investigation. The latter were applied in a synergistic fashion to a major extent in maternity clinics and children’s hospitals by, among others, molecular biologists, clinical geneticists, cytogeneticists, pediatricians, and pediatric pathologists. This article describes a select but small number of the many contributions of pediatrics and pediatric pathology to the current body of medical knowledge.

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1. Introduction

Before the beginning of the 20th century, the child was viewed as a fragile and vulnerable being highly susceptible to infectious agents or undesirable events. The death of a child was endured and often regarded as inevitable, rapidly forgotten, and compensated by a seemingly inexhaustible maternal fertility. The treatises of medicine at the time lingered more on events surrounding delivery than on the evolution of the pregnancy and the state of the newborn or, even less, the fetus, both of whom were remembered (if at all) by the fact that there had been no time to baptize them.

In the middle of the 20th century, enhanced public education regarding pregnancy, together with medical advances, namely, improved measures to prevent and treat neonatal infections, led to the recognition of the value, both present and future, of children and drew attention to their illnesses. Following advances in obstetrical care and improved hygiene in the delivery process and the newborn nursery, pediatrics and pediatric nursing were born.
Similar to the prior century regarding adults, attention was next focused on determining the causes of a child’s death based on pathologic alterations found at autopsy. With improved histopathologic techniques and knowledge acquired from adult pathology, pediatric pathology, in the early years, was little more than an extrapolation and transposition of adult diseases and had a very limited field of investigation. Infections and tumors naturally occupied a major place; however, these sections were buried in chapters pertaining to the pathology of organs, which represented the basis of classification and organization in textbooks on anatomatic pathology of the time. Then, many of the diseases and lesions identified in newborns, infants, and older children did not integrate well in the classical framework of adult pathology.

Beginning in the mid-1900s, the unique nature of pediatric pathology would be discovered and appreciated, little by little. It was recognized that the novelty of pediatric pathology resided in the fact that the affected organs and tissues were close to their embryonic origins and engaged in development, usually spared from deleterious environmental factors. The purpose of this article is to share some of the contributions, past and present, of pediatrics and pediatric pathology to the body of knowledge regarding human diseases. These contributions are grouped under 3 headings:

1. The explosion of knowledge in genetics and the development of molecular methods.
2. Infant immunologic naïveté and vulnerability to infection.
3. The unique nature of pediatric neoplasia.

2. The explosion of knowledge in genetics and the development of molecular methods

Well before the Mendelian laws of heredity were formulated and molecular biology evolved to become the highly advanced discipline it currently represents, major congenital malformations, for example, Siamese twins, anencephaly, hygromas, and massive edema, were surely not oblivious to observers of the time. By their very monstrosity, these malformations gave birth to interpretations varying in degrees of fantasy. More important, they provided material for disease classification and opened the avenue for the study of embryonic development.

First, in embryologic studies in rodents and birds and, later, drosophila, it became evident that interactions of immense complexity were required to allow for the organization of 3 embryonic layers based upon a central common blueprint that included bilateral symmetry and apico-caudal development. Recent investigations dissected part of this complex developmental process and have led to the discovery of the role of some important constitutional genes conserved throughout evolution, such as HOX and TBX1 [1]. This gave birth to the recognition of the critical role of germline mutations as the cause of malformations, such as spina bifida, palatine division, holoprosencephaly, and DiGeorge syndrome. This initial step was essential as it enabled one to distinguish the embryo and malformative embryopathies, for example, DiGeorge syndrome, from the fetus and acquired, not inherited, deforming “dysruption sequence” fetopathies, for example, digital contractures and amputations stemming from amniotic bands. As well, it served to establish a chronologic distinction between malformation and deformation and a simple manner in which to study their diverse etiologies. Later, the systematic practice of autopsies in infants revealed the unexpected incidence of severe malformations, especially those affecting organs in which development was complex, such as the brain, heart, and kidney.

In 1900, a trilocular heart was the first specimen and centerpiece of the Maude Abbott collection of congenital heart disease cases at McGill University (Montreal, Quebec, Canada). Dr Abbott was one of the first pediatric pathologists. The museum she founded was based on the pioneering works of Sir William Osler. This specimen was the first of many that, in time, facilitated the formulation of a cohesive classification of congenital heart defects and provided a foundation for the design of corrective surgical procedures. After Dr Abbott, Dr Frederick W. Wiglesworth, a distinguished pathologist at the Montreal Children’s Hospital (Montreal, Quebec, Canada), maintained and continuously added to the collection from 1946 until 1972. The descriptions of the malformations corroborated those occasionally made by adult pathologists and later by radiologists using ultrasound. Benefiting from a superior technology, the latter demonstrated not only the frequency but also the latency that attends to some conditions, such as single umbilical artery, ureterocele, and annular pancreas.

Rapidly, the extension of the Mendelian laws of genetics to man illustrated that alterations of the genetic message affected not only the initial development of an organ and intimate cell organization but also, and perhaps, more important, the subsequent steps of synthesis and degradation of molecules that are essential for normal ontogeny.

In 1908, Sir Archibald Garrod, an English (London) physician and chemist, delivered the Croonian Lecture before the Royal College of Physicians entitled “Inborn Errors of Metabolism.” This represented an innovative chapter in medical history, one which made possible an understanding of a number of relatively rare human diseases [2]. Alcaptonuria, albinism, pentosuria, and cystinosis were the first disorders to be recognized, thereby, illustrating the novel and informative role of pediatrics and chemistry in the description of new conditions. A mutation may affect a gene implicated in the metabolism of a metal (iron, copper), an enzymatic activity (glucose 6-phosphate dehydrogenase), a protein (hemoglobin, dystrophin), a polysaccharide, a lipid,
or an intermediary molecule, such as the cystic fibrosis transmembrane regulator.

The clinical expression of these “monogenic diseases” is quite varied, depending chiefly upon the tissue distribution of the gene product, the nature (site or magnitude) of the mutation, and the role played by the affected molecule in cellular metabolism. Thus, mutations of a mitochondrial gene involved in the respiratory chain are often expressed at birth, whereas those affecting the structure or metabolism of some amino acids (phenylalanine) or sugars (galactose) manifest months or even years postnatally. Such monogenic diseases have been regarded as “errors of nature,” confirmed by the identification of an abnormal and sometimes measurable protein, the occasional success of substitutive therapy and the phenotype of “knockout” mice for the gene under study. These conditions, in some instances, may be diagnosed at birth or in utero. Appropriately treated, some patients survive to adulthood, for example, cystic fibrosis and α-1-antitrypsin deficiency. Study of the diverse expression of these disorders contributed original information related to the secrets of molecular metabolism and revealed unsuspected alternative pathways. Without cystic fibrosis, the role of the gene for the cystic fibrosis transmembrane regulator might never have been discovered [3].

In short, this class of diseases, discussed in the previous paragraphs, was born essentially in the domain of pediatrics and now occupies an important place that has led to the creation of specialized services in children’s hospitals. In a recent 2245-page, 2-volume excellent and monumental textbook edited by Enid Gilbert-Barness entitled Potter's pathology of the fetus, infant and child, nearly a hundred pages were devoted to “metabolic diseases” [4]. This multiauthored textbook was the product of years of acquired information, building on the original work of Edith L. Potter in 1952.

Commensurate with the development of pediatric pathology as a specialty and, indeed, a culture, a number of pediatric pathology societies evolved. As the societies took form, journals, textbooks, and fellowship training programs in pediatric pathology took root. In 1990, the American Board of Pathology offered its first examination in the newly declared subspecialty of pediatric pathology.

Pediatrics made a significant contribution to diseases stemming from chromosomal abnormalities. In 1959, Jérôme Lejeune, a pediatrician and geneticist in Paris, and colleagues [5] reported that Down syndrome was associated with trisomy of chromosome 21. This landmark discovery opened a new chapter in pediatrics, medicine, and genetics and shed light on the origin of a certain number of genetic conditions to be described in the coming years. The documentation of a monosomic deletion or translocation based on a peripheral blood leukocyte or skin and/or fascia lata fibroblast culture karyotype subsequently opened antenatal diagnosis (amniocentesis and chorionic villus sampling), enabling one to localize and analyze genes in the fetus and infant. In due course, these techniques and others were applied to infantile and adult tumor pathology.

Rapidly, it became evident that light microscopic chromosomal anomalies were but one expression of major genetic anomalies in which invisible, more subtle lesions are represented by mutations, deletions, repetitive sequences, and others. These genetic alterations might impact not only on structural genes but also and often on regulatory genes and those encoding transcription factors.

Genetic studies conducted essentially in plants and animals permitted one to develop and perfect techniques capable of exploring the genetic polymorphisms of an individual, for example, single nucleotide polymorphisms, to analyze the 3 million base pairs that constitute the human genome and to isolate some of the 25 000 to 30 000 human genes to establish the correlations between variations of genotype and different expressions of phenotype. Because these techniques require only a tiny amount of genetic material, they are widely applicable in pediatrics where they have demonstrated their value in discovering unexpected genetic variations and aberrations. Although these techniques are tedious and labor intensive, they are capable of detecting fetal DNA (3%-6% levels) in the maternal circulation [6].

Today, the infant, generally spared of noxious environmental events, has proved to be an important field of study. As an example, it has been established that mutations of CARD15, a gene that normally encodes for NOD2, a protein expressed by macrophages involved in the recognition of microbial agents, are implicated in the etiology of Crohn’s disease [7]. Along the same line, it has been established that certain HLA groups, such as DQ2/DQ8, are frequently associated with celiac disease in infants [8]. Therein could reside a potential approach to the complex polygenetic conditions of adulthood. Again, diseases in the infant and child are a rich field of study for conditions that affect adults.

As well, across the extreme polymorphism of the human genome, the notion has arisen that some genetic sequences may act as biomarkers for exquisite drug hypersensitivity and explain isolated and undesirable severe drug reactions stemming from a genetic inability to properly metabolize the drug [9].

It is our conviction that, in some instances, pediatrics and many of its diseases offer excellent models that allow for a better understanding of conditions of unknown pathogenesis. Four are cited.

(a) Mutations in FOX P3 (Xp11.23) have been identified in a rare and lethal pediatric syndrome called IPEX (immunodeficiency, polyendocrinopathy, enteropathy, X-linked) characterized by diverse autoimmune phenomena. The scurfy mouse, described in 1959, shares many similarities with boys with IPEX. In murine studies, FoxP3 is normally expressed by regulatory CD4+CD25+ T cells that contribute to the maintenance of immune tolerance. Interestingly, FoxP3 is
overexpressed in nonrejected allografts, confirming its
tolerogenic role, thereby providing a new approach to
monitor allograft rejection [10].

(b) Robert P. Bolande, a creative pediatric and experimental
pathologist, presented in 1974 [11] and redefined in
molecular terms in 1997 [12], a novel, groundbreaking
concept: “the neurocristopathies.” Among a diverse
group of afflictions, he recognized a common thread:
the affected tissues were derived from the neural crest.
Some of these conditions included neuroectodermal
tumors, certain endocrine tumoral syndromes, Hirsch-
prung’s disease, and a syndrome of dysautonomia with
congenital central hypoventilation, known as Ondine’s
curse. The recent discovery of mutations in PHOX2B
that controls the expression of the RET gene, more
directly implicated in familial forms of Hirschprung’s
disease and the tumoral syndromes, multiple endocrine
neoplasia (MEN) 2A/B, has given a molecular
confirmation to Ondine’s curse and Bolande’s propheti-
cal conceptualization [13,14].

(c) Progeria of Hutchinson-Gilford, characterized by
infantile premature aging, is associated with anomalies
in the nuclear membrane linked to mutations in LMN
(laminin and nuclear antigen) that encodes for
progerine. This protein can be identified in fibroblast
cultures from older individuals, thereby, opening an
avenue of novel research on aging [15].

(d) Most of the chondrodysplasias, from achondroplasia to
dyschondrosteosis, and certain acromegalic dysplasias
have been found to have an original molecular
signature, illustrating that different mutations of the
same gene can produce variable phenotypes.

If the molecular approach brings many new elements to
the evaluation of susceptibility factors and the distinction
between those innate and acquired, the impact of the
environment, nutritional deficiencies, and deplorable socio-
economic conditions have not been consistently included in
these studies: these factors are likely to impact on
development of the embryo and fetus as well.

Retrospective epidemiologic studies revealed that infants
with retarded fetal growth and small for gestational age
appear to be at increased risk for metabolic disorders, such as
type 2 diabetes mellitus, dyslipidemia, hypertension, cor-
ronary atherosclerosis, and psychiatric disorders later in life
[16]. Other epidemiologic studies, as well as animal studies
based on the ligature of the uterine arteries, have tended to
support this association. Once more, this illustrates that
certain diseases of adults take root in utero, as supported by
the ultrasound finding of thickening of the aortic arch in the
fetus and infants with development delay [17]. A systematic
study of blood lipids in 599 adolescents discovered 2
children with unsuspected familial hypercholesterolemia. In
addition, in a number of children, the serum lipid levels were
abnormal, and this opened the debate about using screening
tests in adolescents [18]. These represent additional
unexpected contributions of pediatrics and pediatric pathol-
ogy to adult pathology and preventive medicine.

3. Infant immunologic naïveté and vulnerability to infection

Pediatric pathology has contributed substantially to the
identification of infectious agents and their diversity.
Because the infant may become massively infected during
a vaginal delivery and because newborns and young infants
are immunologically naive, they can be easily infected and
may die of microbial diseases an adult could combat
without difficulty.

Infections caused by Herpes simplex viruses, Cytome-
galoviruses, Parvovirus, Toxoplasma, and Listeria are often
generalized and fatal in the fetus and newborn. As the
embryonic egg constitutes an ideal culture milieu for
certain viruses, the fetus is highly vulnerable to agents
such as Cytomegalovirus and Parvovirus 19. In 1954,
Pneumocystis carinii was identified in lung sections with
pneumonitis rich in plasma cells in infants within a
confined community [19]. Epidemics of bronchopneumo-
nia or diarrhea affecting newborns in the nursery led to the
discovery of adenovirus and respiratory syncytial virus as
the cause of the pneumonias and Rotavirus, Coronavirus,
and Escherichia coli as the agents responsible for the
diarrhea [20].

Cultures of an “epidemic” lymphoma affecting the jaw
(mandible) of children in sub-Sahara Africa subjected to
biopsy by Sir Denis Burkitt [21] were found in 1964 to
contain a Herpes virus in the laboratory of Sir Michael
Anthony Epstein: the virus was later called the Epstein-Barr
virus (EBV) [22]. In due course, this virus was identified as
the etiologic agent of infectious mononucleosis. Several
years later, EBV was found to be important in the X-linked
lymphoproliferative (XLP) syndrome, a rare condition
described by David T. Purtilo, a pediatric pathologist [23].
In boys with a mutation in the XLP gene, infection by EBV
leads to the development of 1 of 5 phenotypes; the most
common (58%) is fulminant infectious mononucleosis.
Mutations of the XLP gene likely contribute to fulminant
infectious mononucleosis, a condition characterized by
immunologic anarchy and death usually within 1 month
after infection with EBV.

Noteworthy is that adolescents were the first chosen to be
vaccinated: James Phipps, smallpox vaccination in 1796 by
Edward Jenner, and Joseph Meister, rabies vaccination in
1885 by Louis Pasteur. These adolescents offered by their age
and acceptance a terrain for observation to judge the protection
brought about by this risky inoculation that contributed to
molding the early concepts of defensive immunity.

The initial descriptions of genetically determined primary
immunodeficiencies were in infants and children. The
contributions of Robert A. Good, a prolific and creative
pediatric immunologist, tower above all others. For one such condition, chronic granulomatous disease, Benjamin H. Landing, a brilliant pediatric pathologist, reported the initial description of pigmented macrophages in tissues of children with a syndrome of recurrent infections [24]. Not long thereafter, the pathogenesis of this disease was elucidated by the group led by Good [25]. Several years later, a clinical report described several newborns with neonatal tetany and impaired cellular immunity. At autopsy, they lacked a thymus and parathyroid glands and some had cardiac and great vessel abnormalities. In due course, this came to be known as the DiGeorge syndrome, named after the astute pediatric endocrinologist who described the condition [26]. Another clinical report at this time described a male infant with failure to thrive, repetitive serious infections, profound lymphopenia, but with serum immunoglobulins and the presence of plasma cells in tissues. In this child, the thymus was dysplastic: minute, devoid of Hassall corpuscles, and depleted of thymocytes [27]. In due course, the failure of the thymic epithelium to differentiate and mature came to be recognized as the morphologic hallmark of severe combined immunodeficiency. These 2 reports supported the experimental studies by Robert Good [28] in Minneapolis and Jacques Miller [29] in London on the critical role of the thymus in lymphocyte ontogeny, which led to the formulation of a dual immune system composed of T and B lymphocytes.

At the other end of the spectrum and many years earlier (in 1907), excessive reactions of the immune system were described by Clemens von Pirquet, a pediatrician and scientist at St Anna’s Children’s Hospital in Vienna, Austria, who defined and coined the term allergy [30].

Hence, the contributions of pediatrics, pediatricians, and pediatric pathology to the knowledge and diversity of infectious human diseases; their control by vaccination; and the dissection of the immune system are milestones in medical history.

4. The unique nature of pediatric neoplasia

By their very nature, tumors in the infant and child have contributed substantially to an understanding of the pathogenesis of neoplasias. Carcinomas are exceptional in children. In contrast, leukemias (usually lymphoid), embryomas (tumors of blastema), gliomas, teratomas, and soft tissue and osseous sarcomas dominate. These tumors are remarkable, as they exhibit traits of the embryonic tissues from which they are derived. This is not illogical, given that embryonic tissues are rapidly proliferating and differentiating, a process that continues (depending on the organ or tissue) several years postnatally. Leukemias aside, most notable are tumors of blastema including nephroblastoma of the kidney (Wilms’ tumor), neuroblastoma of the adrenal medulla, sympathetic ganglia and organ of Zuckerkandl, medulloblastoma of the cerebellum, hepatoblastoma of the liver, and ocular retinoblastoma. Mutagenic environmental factors so often implicated in adult tumors are not applicable in most of these instances.

In a small number of children, one or several malformations may be evident at birth and the same child later on (usually several years) develops a neoplasm. This led to the concept of Teratological and Oncological Associations. Indeed, several syndromes bear witness to this association: Aniridia-Wilms’ syndrome and WAGR syndrome (Wilms’ tumor, aniridia, genital malformations, and growth retardation) and the Beckwith-Wiedemann overgrowth syndrome with Wilms’ tumor and hepatoblastoma, most commonly. These findings suggested an interruption in genetic messages that contributes to the malformation and neoplasm. With the passage of time, WAGR and Aniridia-Wilms’ tumor syndromes are now known to represent contiguous gene or microdeletion syndromes [del(11)(p13)], in which deletions impact negatively on contiguous genes to produce the syndrome. The Beckwith-Wiedemann syndrome is now ascribed to aberrant genomic imprinting at 11p15. Here again, the concepts of contiguous gene deletion syndrome and genomic imprinting are derived, in large measure, from pediatrics.

In the soil of childhood neoplasia arose the notion of oncogenes and antioncogenes, the latter known as tumor suppressor genes. Mutations of these genes are now associated with many tumors of children and adults. One of the most recognized associations is the Li Fraumeni syndrome, in which affected children and adults inherit a germline mutation of one allele of the tumor suppressor gene TP53. These individuals are at increased risk for developing acute leukemias, soft tissue and osseous sarcomas, gliomas, breast cancer, and adrenal cortical carcinoma, among other neoplasms.

In studies of retinoblastoma, the loss of genetic information on the long arm of chromosome 13 (13q−) appeared to be central to the pathogenesis of the tumor. Eventually, the retinoblastoma gene (RBI) was mapped to 13q14 and, after PT53, became the second described tumor suppressor gene.

This leads to the seminal works of Alfred G. Knudson Jr, a pediatric endocrinologist and epidemiologist, who formulated (in 1971) his prescient “2-hit hypothesis” regarding the oncogenesis of familial and sporadic retinoblastomas [31]. The term hit refers to a mutation. The induction of cancer requires that both alleles of a gene (eg, a tumor suppressor gene) be mutated. It has since been reported that the initial steps in the oncogenic process are marked by the reappearance or reactivation of the expression of certain genes, such as the cyclins, implicated transiently in normal tissue or organ development [32]. The dedifferentiation or anaplasia seen in some of these embryonic tumors demonstrates “the reciprocal dance between cancer and development [33].”

Teratomas can reproduce a spectrum of tissues, mature but also extremely immature, including choroidal and vitelline tissues. Axial teratomas in the infant are a perfect
illustration of “the reciprocal dance between development and cancer.” One of the first stem cell lines to be described, “EC” for embryonal carcinoma, was derived from a murine line of testicular teratocarcinoma established by the group led by Leroy Stevens.

Whereas the anomalies in genetic messages are most often cryptic and only detectable with molecular methodologies, some are more apparent, recognized by chromosomal numerical and structural alterations. The first malignancy in which a chromosomal anomaly was defined was chronic myelogenous leukemia—the “Philadelphia” chromosome. This report was, to cancer cytogenetics, the equivalent of Lejeune’s contribution to medical cytogenetics about Down syndrome 1 year earlier. Ewing sarcoma was the first solid malignant pediatric tumor to demonstrate a characteristic cytogenetic finding described concurrently in 1983 by Alain Aurias [34] and Claude Turc-Carel [35]. It turns out that in many pediatric malignant neoplasms, the neoplastic cells feature consistent cytogenetic aberrations, unlike adult neoplasms that tend to have considerable variability in regard to genetic alterations. This might be explained by the fact that pediatric malignant neoplasms are largely determined by hereditary rather than environmental factors.

These discoveries opened an avenue of research in oncology that now includes diverse techniques: conventional cytogenetics, fluorescence in situ hybridization, comparative genomic hybridization, the analysis for aberrant fusion transcripts with reverse transcriptase, and the polymerase chain reaction and DNA and expression microarrays.

5. Concluding remarks

Thus, by its novelty, apparent simplicity, relative immunity from noxious and deleterious environmental factors, the important role played by heredity, the course of time, and the events of early life (in utero) contributions from pediatrics and pediatric pathology have brought a significant body of knowledge to human disease—today prophylactic, tomorrow predictive.

In this brief review, we have described some of the contributions of pediatrics and pediatric pathology to the body of medical knowledge. With reflection, one must conclude that much of this knowledge stemmed, to a large extent, from the synergy among pediatricians, obstetricians, radiologists, pediatric surgeons, biochemists, cytogeneticists, medical geneticists, molecular biologists, immunologists, epidemiologists, and pediatric pathologists grouped and working in maternity clinics and hospitals devoted to the care of children. This close and natural collaboration between diverse disciplines represents “translational research” at its best. It is anticipated that such groups will continue to probe research issues in sick infants and children and will be central to innovative research and advancements in pediatrics.

Over the past half century, pediatric pathology has become a field of its own with distinct societies, journals, fellowship training programs, and a specialty examination administered and certified by the American Board of Pathology. As a discipline, pediatric pathology is vastly different from adult pathology. The differences reside in the very nature of the material in pediatric specimens, as discussed in this review. Accordingly, most children’s hospitals are staffed by fellowship-trained pediatric pathologists. However, some medical centers not devoted exclusively to children may not have the services of a trained and experienced pediatric pathologist, as the number of such individuals is well below the need. In these settings, pediatric pathology material will be examined by adult trained pathologists. In large measure, it was for this audience that this article was written: namely, to expose the adult pathologist briefly to the unique nature of pediatric pathology. It is to be hoped that this will encourage consultation when unusual pediatric pathologic material presents.

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