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LECT 1

MYTHOLOGY AND GENETICS

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Congenital malformations affect about 1 in 33 newborns worldwide, and their occurrence has been reported during the entire human history. The interest in congenital malformations and their possible causes reaches back over many millennia, and people of a given era tried to explain the birth of affected children based on the contemporary state of knowledge, contemporary philosophical ideologies, and, importantly, the religious beliefs of the period [1]. The oldest information on congenital malformations has been recorded going back at least as far as 1500 BC, when these conditions were believed to represent portents of future events, but the most interesting interpretations of birth defects are related to Greek mythology, where different diseases, such as cyclopia, disorders of sex development, mental retardation, malformations in twins, were interpreted as determined by the will of the Gods. Greek mythology represented the diseases, the malformations and the transmission of such conditions as the consequence of fate, sins, divine intervention or inheritance. Surprisingly, over 2000 years later, Omics sciences, although based on a completely different knowledge, still debate a similar question: how much of our destiny is written in our genes and how much, on the other hand, can be modified? The aim of this presentation is to compare the mythologic tale and the scientific knowledge about genetic conditions, by analysing how some ancient representations of human body, human diseases and predestination can be revaluated in light of modern knowledge on genetic variability, disease risk, penetrance and epigenetics. The presence of a genetic variant does not invariably mean that a specific disease will occur, and our genome does not represent an unmodifiable program. On the contrary,

the genetic information is able to interact with the environment, lifestyle and biological context, and to modify its own activity. In this view, the passage from “the destiny written by Gods” to the “destiny written by genes” represents a powerful metaphor but also a communicative risk: genetics, in fact, can be easily interpreted as a modern determinism similar to the one of ancient mythologic tales.

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LECT 2

THE ITALIAN DEMOGRAPHIC CRISIS: FROM PAST TO FUTURE

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In his novel “2024” the French writer Jean Dutourd describes a dystopian world without children; the book was written back in the 1970s but the title today sounds unsettlingly prophetic. Nowadays, in 2026, it is natural to wonder how closely Italian reality is approaching that alarming scenario.

Data provided by the Italian National Institute of Statistics show a worsening demographic decline that currently does not seem likely to be reversed. Italy is becoming an increasingly old country, where people over 65 are almost twice as many as children under 14, and those over 80 outnumber children under 10. A declining birth rate is a phenomenon common to most economically developed countries, and its roots lie in the great social transformations that followed the Second World War, particularly the progressive shift away from agriculture and the massive urbanization that came with it.

Since the 1960s, female emancipation has grown steadily, together with women's education and their participation in the labor market. This has deeply reshaped the structure of Italian families and significantly affected their reproductive capacity. As a result, the fertility rate of women living in Italy has fallen since the early 1970s, reaching its lowest points first in 1995 (1.19) and then in 2025 (1.14) with a progressive reduction of the population, especially among the youngest and the most economically active groups.

Inevitably, all this will have an impact on our welfare state in the medium term. Some of the

social achievements we now take for granted could become unsustainable: our universal healthcare system, a free public education, and a pension system that guarantees a dignified retirement for all.

At this point, what can be done to address the problem? All Western countries have invested significant resources to address the demographic crisis, mainly through three policy areas aimed at supporting the birth rate:

1. measures to promote the independence of young people (incentives for first home or rent, youth and female employment initiatives, training programs);
2. actions to help parents to balance work and family life (public childcare services, extended mandatory paternity leave, flexible working hours and smart working);
3. interventions to strengthen family income (tax reductions, financial aid to cover childcare costs, and long-term continuity of income support).

None of these strategies alone seems decisive, but combined, they can change the demographic trend, especially when paired with well-designed migration policies based on clearly defined flows agreed with countries of origin, and interventions that encourage effective integration of migrants and their families into our society.

In line with this, it is worth noting that, since the baby boom, the only period in which the birth rate in Italy showed a significant increase was during the 2000s, mainly due to the massive migration from Eastern Europe following the collapse of the Soviet Union.

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LECT 3

CLIMATE CHANGE: WHAT ARE THE EFFECTS ON PERINATAL HEALTH?

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Climate change is now one of the major emerging threats to maternal and child health. Fetal life and the perinatal period constitute particularly sensitive developmental windows during which exposure to

environmental stressors can have profound effects. Extreme temperatures, heat waves, and air pollution – which often occur concurrently – are associated with a wide range of adverse pregnancy and neonatal outcomes through mechanisms involving maternal heat stress, impaired placental function, systemic inflammation, and oxidative stress.

The joint WHO-UNICEF-UNFPA report on protecting maternal, newborn, and child health from climate change identifies an increased risk of gestational diabetes, hypertensive disorders of pregnancy, preterm birth, low birth weight, and stillbirth among the main consequences of exposure to climate-related hazards, including extreme heat [1]. An umbrella review published as part of the World Health Organization's initiative on climate change across the life course quantified these effects: the risk of preterm birth increases by 16% during heat waves compared with non-heat-wave days, whereas exposure to fine particulate matter (PM_{2.5}) reduces mean birth weight by approximately 22 g for every 10 µg/m³ increase in concentration. An estimated 15.6% of low-birth-weight cases worldwide are attributable to this pollutant. The risk of stillbirth is also associated with heat exposure, while congenital heart defects are the structural anomalies most frequently reported in association with prenatal exposure to air pollution [2]. Furthermore, a meta-analysis of 198 studies conducted in 66 countries confirmed a dose-response relationship between heat exposure and neonatal outcomes, with a 48% increase in the risk of congenital anomalies at the highest exposure levels (odds ratio, 1.48; 95% confidence interval, 1.16-1.88) [3].

This presentation will review selected epidemiological evidence and pathophysiological mechanisms linking the climate crisis to perinatal health. Particular attention will be given to the potential protective role of greener urban environments, as exemplified by the “3-30-300” principle: being able to see 3 trees from one's home, living in a neighborhood with at least 30% tree-canopy cover, and having access to high-quality green space within 300 meters have been associated with an improved quality of life. The presentation will also emphasize the need for targeted adaptation and mitigation policies designed to protect the earliest stages of life. Finally, the implications for neonatal clinical practice and future research will be discussed from a One Health perspective that places newborns at the center of strategies addressing the climate crisis.

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LECT 4

PRIMARY ATOPIC DISORDERS: CLINICAL AND MOLECULAR SPECTRUM AT THE INTERFACE OF ALLERGY AND INBORN ERRORS OF IMMUNITY

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The association between severe atopy and primary immunodeficiency was recognized as early as 1978, when Burgio et al. proposed that severe atopic manifestations might represent a form of immunodeficiency. In 2018, Lyons and Milner formally introduced the term “primary atopic disorders” (PAD) to describe a heterogeneous group of monogenic inborn errors of immunity (IEI) characterized by severe and/or multiple allergic manifestations, providing a unifying framework for previously recognized disorders sharing a prominent atopic phenotype. PAD represent a distinctive interface between common allergic diseases and classical IEI. Their pathogenesis involves dysregulation of allergic effector responses, often associated with exaggerated type-2 inflammation. Increased IgE levels, eosinophilia, abnormal mast-cell activity and Th2-skewed immune responses are frequent immunological features. Importantly, the clinical expression of PAD is not restricted to allergy, as many patients may develop additional manifestations of immune dysfunction, including susceptibility to infections, autoimmunity, malignancy, growth impairment and other systemic abnormalities. The complexity of PAD reflects the involvement of

different immune pathways and the marked clinical heterogeneity of these disorders. The molecular classification proposed by Lyons et al. groups PAD according to the principal mechanisms underlying disease, including defects in T-cell receptor signaling and cytoskeletal remodeling, cytokine signaling, T-cell repertoire restriction, immune tolerance, cellular metabolism, skin-barrier function and mast-cell dysregulation. To facilitate clinical recognition, Castagnoli et al. proposed a phenotypic classification of PAD, grouping these disorders into distinct clinical categories, including Hyper-IgE syndromes, Omenn syndrome, Wiskott-Aldrich syndrome (WAS) and WAS-like disorders, IPEX and IPEX-like conditions, and CBM-opathies and other miscellaneous disorders. Distinguishing PAD from common, non-syndromic allergic diseases remains challenging because of their substantial clinical overlap. Severe or multiple atopic manifestations, particularly when associated with early onset, marked eosinophilia or elevated IgE, recurrent or unusual infections, growth impairment, gastrointestinal disease, autoimmunity or other systemic features, should prompt consideration of an underlying monogenic IEI. Early recognition is essential, as diagnostic delay may result in substantial morbidity and may adversely affect long-term outcomes. PAD represent a heterogeneous group of IEI in which severe atopy may be the presenting or dominant clinical feature. They occupy a continuum between classical immune deficiency and common allergic disease, challenging the traditional separation between immunology and allergy. Integrating molecular and phenotype-based approaches may facilitate recognition of these disorders and support earlier diagnosis and individualized management.

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LECT 5

NEW PRECISION THERAPIES IN PEDIATRIC RHEUMATOLOGY

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The year 2000 marked the beginning of the so-called “biologic era” in the management of pediatric rheumatic diseases (PRD). The discovery of mediators and mechanisms involved in the immunopathogenesis of these conditions has led to the development of several therapeutic agents that target specific pro-inflammatory cytokines or inflammation pathways. Some of these drugs have been tested or approved for use in clinical care. The application of a treat-to-target strategy, which is based on explicitly defining a treatment target and applying tight control and necessary therapeutic adjustments to reach the target, can make the overall therapeutic approach more rational and improve disease outcomes. After the success obtained in the hematology field, CAR-T cell therapy has recently emerged as a promising therapeutic option for systemic autoimmune diseases. This procedure is based on genetic engineering of autologous T cells to express synthetic receptors that recognize specific antigens on B cells, most frequently CD19 or B-cell maturation antigen. Through the elimination of these cells, which are key determinants of the autoimmune process, this therapy may potentially “reset” immune homeostasis and switch off the disease process. The first experiences with the use of CAR-T therapy in patients with refractory PRD have been very encouraging, with most patients achieving complete drug-free remission. A wide range of innovative “off-the-shelf” therapeutic modalities are emerging, including allogeneic cell products that eliminate the need for *ex-vivo* cell manipulation, CAR constructs based on different effector cells, such as NK cells, targeted lipid nanoparticles that deliver genes encoding B-cell targeting CARs directly to a patient’s effector cells, and bi-specific and tri-specific antibodies, capable of engaging two or even three different antigens simultaneously. Another promising area of research is the creation of regulatory, rather than cytotoxic, CAR-T cell therapies. These compounds are aimed to retune rather than to reset the immune system, that is, instead of eradicating autoreactivity, they retune it back to the healthy state. This advance, together with improved patient stratification and identification of novel diagnostic and prognostic biomarkers, has transformed the treatment landscape of PRD by fostering the implementation of precision medicine and personalized therapeutic

approaches, with the ultimate goal of reaching sustained, glucocorticoid-free disease remission. Several unmet needs remain, however, such as the lack of evidence-based recommendations for medication discontinuation after the achievement of sustained remission and of suitable protocols for patients who do not respond adequately to the contemporary interventions. There is, thus, the need for additional interdisciplinary, inclusive and translational research to further improve the outcome and quality of life for young people living with these challenging diseases.

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LECT 6

GENETICS OF NEONATAL STROKE

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Perinatal stroke constitutes a well-defined group of cerebrovascular diseases causing early brain damage, and represents the most common cause of hemiparetic cerebral palsy. Two clinically distinct modes of presentation are recognized. Acute perinatal stroke occurs in newborn infants at or near birth, typically presenting with focal seizures or encephalopathy. Presumed perinatal stroke refers to chronic infarcts diagnosed in a delayed manner. Neonatal arterial ischemic stroke (NAIS) is the most frequent subtype, with an incidence estimated at 1 in 3,000 live births. The middle cerebral artery (MCA) territory is involved in 80-90% of cases. The most common presenting symptom of acute neonatal stroke, particularly NAIS, is focal seizures. Other acute manifestations include hemiparesis (rare at birth), lethargy, hypotonia, and apnea. From a pathophysiological standpoint, NAIS may

be broadly classified into two categories based on exposure to perinatal inflammation:

1. embolism-associated NAIS, occurring in neonates not exposed to perinatal inflammation, in which cardiac or placental embolic mechanisms predominate;
2. arteritis-associated NAIS, occurring in neonates exposed to perinatal inflammation, defined by a composite criterion including maternal fever, histological chorioamnionitis, or early-onset neonatal infection; in this category, inflammatory arteriopathy is the proposed underlying mechanism.

At 7 years of age, 57% of children with NAIS present at least one neurological sequela: 46% language disorder, 31% cerebral palsy, 26% school difficulties, 11% active epilepsy, and 8.5% global cognitive impairment. Although several maternal, placental, perinatal, infectious, cardiac, and hematological risk factors have been described, a relevant proportion of neonatal stroke cases remains unexplained after standard diagnostic evaluation. In this context, genetic and monogenic causes are increasingly recognized as potential contributors to neonatal cerebrovascular disease. The increasing availability of next-generation sequencing (NGS), targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS) has expanded the possibility of identifying rare monogenic causes of neonatal and perinatal stroke. In parallel, metabolomic approaches may provide additional diagnostic information, particularly when stroke is part of a broader metabolic or multisystem disorder. An Italian multicenter group of neonatal neurology experts is currently conducting a systematic review. Its primary objective is to identify and summarize the genetic and monogenic causes of neonatal stroke reported in the literature from 2006 to 2026. The review will synthesize the available literature on genetic contributors to neonatal stroke, with the final aim of proposing an evidence-informed diagnostic workflow.

LECT 7

CONGENITAL HEART DISEASE AND SYNDROMES

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Congenital heart disease (CHD) is the most common form of birth defect, with an estimated incidence, according to the most recent data, of approximately 1% of live births [1]. It comprises a heterogeneous set of structural anomalies of the heart and/or major blood vessels resulting from disorders of embryonic development. The etiology of CHD is complex, with risk factors such as exposure to teratogenic or environmental agents, chronic maternal pathologies, nutrition, and genetic abnormalities having been identified. Among the genetic causes, the main one is aneuploidy, or the variation in the number of chromosomes compared to the normal diploid set [2]. Along with aneuploidy, CNVs represent another significant source of genetic variation. These are deletions or duplications of DNA segments, ranging from a few thousand to several million bases, which alter the dosage of the genes involved. CNVs vary in size, number of genes involved, and phenotypic impact, and many are linked to recognized syndromes, in which CHD is a recurrent feature. A study was conducted that analyzed data from 626 pediatric patients treated at the Pediatric Cardiology Outpatient Clinic of the Cagliari University Hospital between 2014 and 2025. The study included children with structural CHD. Of the 626 patients assessed, 370 met the inclusion criteria for structural CHD, 179 (48.38%) males and 191 (51.62%) females. Of these, 17% had a syndromic condition or genetic abnormality. Down syndrome was the most common associated genetic condition (39.7%), followed by Noonan syndrome (15.9%). DiGeorge syndrome and Williams syndrome followed (both 7.9%). Analysis of congenital heart defects in the subgroup of patients with Down syndrome (n = 25) confirms the existence of an extremely specific and well-established phenotypic association in the literature [3]. The most significant finding is the clear prevalence of atrioventricular defects, found in 56% of patients with Down syndrome (14/25). Ventricular septal defects represent the second most common group (28%). Interestingly, the prevalence of conotruncal forms, such as Tetralogy of Fallot (8%), while less frequent than septal defects, is still higher than that found in the general nonsyndromic population, confirming a genetic predisposition of Trisomy 21 toward specific alterations in the development of the endocardial cushions and the cono-trunk.

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LECT 8

APPROACH TO HEREDITARY METABOLIC DISEASES IN THE NEWBORN

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Inborn errors of metabolism (IEM) in neonatal age must be suspected promptly because of the rapidly progressive course and the several existing therapies. The newborn screening programs allow the detection of several treatable IEM, but in some of them the results can be available when the metabolic derangement has already occurred. Other IEM are not included and can still present symptoms during the first month of life.

Signs and symptoms of IEM are usually nonspecific in the first weeks of life: newborns can present with feeding difficulties, vomiting, dyspnea, altered consciousness or frank encephalopathy, hypotonia or seizures. In intoxication-type IEM, there is an asymptomatic period of at least several hours or days, since it takes time for an intoxicating substance to accumulate after dietary exposure. IEM should be considered in case of unexplained neurologic symptoms, particularly if these are progressive. They also should be considered in the setting of specific laboratory findings in first tier metabolic surveys, such as hypoglycemia, hyperammonemia, ketosis, hyperlactatemia or high-anion gap metabolic acidosis. Specific organ involvement must be investigated, as: liver enlargement, icterus or hepatic insufficiency; cardiac manifestations as hypertrophic or dilated cardiomyopathy and arrhythmias; renal disease and tubulopathy; even multiorgan failure as Reye-like syndrome.

Dysmorphic characters of malformations as renal cysts can even be associated to some IEM. Suspicion leads to second tier test as blood acylcarnitines and amino acids, urinary organic acids with orotic acid. They can include some enzymatic tests and other specific biochemical tests. Genetic confirmation follows, usually through NGS panels or WES.

Therapy is disease specific and related to the metabolic derangement. Initial management should ensure adequate cardiorespiratory function and diuresis, reverse catabolism, and reduce exposure to harmful nutrients. Hemodialysis to remove harmful small molecules is reserved in severe conditions for specific biochemical values. Specific disease therapies include: diet (normal, low-protein, controlled carbohydrate intake or high glucose intake, lipid restriction), administration of cofactors (ex. B6 for pyridoxine-responsive encephalopathy) and especially detoxifying medications (as sodium benzoate or carnitine). In few cases enzymatic therapies are available.

In conclusion, for most IEM the early recognition allows rapid management and possibly therapy, modifying life prognosis and disease natural history. Therefore, once common causes have been ruled out, treatable metabolic diseases should be considered promptly.

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LECT 9

UPDATE ON NEONATAL PAIN MANAGEMENT

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Neonatal pain is a major clinical and ethical challenge in contemporary neonatal care. Although newborns, including very preterm infants, cannot verbally communicate their experiences, current evidence demonstrates that they possess functional nociceptive pathways and are capable of experiencing pain. This is particularly relevant in Neonatal Intensive Care Units, where premature and critically ill infants may undergo numerous invasive procedures during a critical period of

brain development. Repeated exposure to painful stimuli has been associated with alterations in stress responses, brain maturation, and neuro-developmental outcomes, although these effects may be influenced by prematurity, illness severity, and medical treatment [1].

Effective pain management begins with prevention. Unnecessary procedures should be avoided, and care activities should be appropriately organized. Non-pharmacological interventions, including breastfeeding, skin-to-skin contact, facilitated tucking, non-nutritive sucking, and sweet-tasting solutions such as sucrose, can reduce behavioral and physiological responses to several minor painful procedures [1, 2]. Parental involvement is increasingly recognized as an integral component of neonatal pain management, with potential benefits for both infant comfort and parental self-efficacy [2].

Because neonates cannot verbally report pain, assessment relies on behavioural and physiological indicators incorporated into validated multi-dimensional pain scales. No single tool is optimal for all clinical situations, particularly in extremely preterm, critically ill, or sedated infants [3]. Pain assessment should therefore be systematic, individualized, and repeated before and after painful procedures.

Pharmacological treatment is required for moderate-to-severe pain, major invasive procedures, and postoperative or prolonged pain. The choice of analgesic should be individualized according to gestational and postnatal age, clinical condition, pain intensity, and expected duration of exposure. Opioids may be necessary for significant pain but require careful dosing and monitoring because of their potential adverse effects and the developmental variability of neonatal pharmacokinetics [1].

A contemporary approach to neonatal pain management requires systematic assessment, prevention, multimodal treatment, and continuous reassessment. Standardized protocols, healthcare professional education, appropriate use of non-pharmacological and pharmacological interventions, clinical auditing, and parental involvement are essential to translate evidence into routine practice. Neonatal pain management should be considered an integral component of safe, ethical, and developmentally appropriate care, ensuring that every newborn receives timely, evidence-based pain prevention and treatment.

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LECT 10

EMERGENCY TRANSPORT OF THE CRITICALLY ILL NEONATE: FROM GROUND TO AIR TRANSPORT. THE ROLE OF NETS AND THE PECULIARITIES OF FLIGHT

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INTRODUCTION

Emergency transport of the critically ill neonate (Neonatal Emergency Transport Service – NETS) represents a fundamental component of the perinatal care network, enabling the safe transfer of the unstable patient from a peripheral center (SPOKE) to a higher level referral center (HUB), while ensuring continuity of intensive care throughout the transfer. The effectiveness of the system depends on standardization of vehicles, dedicated staff training, and adaptation of care strategies to the transport modality used.

AIM

To describe the role of NETS in the management of the critically ill neonate and to analyze the main differences between ground transport (ambulance) and air transport, with particular attention to the physiological and technical-organizational peculiarities of the latter.

DISCUSSION

Ambulance transport ensures pressure continuity and direct access to the patient, but is limited by travel time and road conditions in long-distance or interregional transfers. Air transport, reserved for longer distances or situations of particular urgency, introduces specific physiological variables related to cruising altitude: cabin pressurization, typically maintained at an equivalent altitude of 1,500-2,500 meters (or at sea level in the most critical cases), can induce relative hypoxia, expansion of gases within body cavities, and effects on thermoregulation, which are particularly relevant in the preterm neonate. In addition, there are logistical constraints (limited space, vibration, noise, the need for electromedical devices and transport incubators certified for aeronautical use) and regulatory requirements

(CEN1789, SAE J3043 standards, EASA/ENAC certifications), which call for dedicated equipment and staff with specific neonatological training.

CONCLUSIONS

Although burdened by greater organizational complexity and specific altitude-related physiological challenges, air-based NETS represents an indispensable tool for ensuring equitable access to neonatal intensive care on a regional/national scale, provided there is rigorous technical and training standardization of the crews.

LECT 11

THIRTY YEARS OF NORMAN NEONATOLOGY, PEDIATRIC, AND NURSING CONFERENCES

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INTRODUCTION

Introducing new ideas and projects in a firmly traditional environment was certainly not easy. However, good fortune and, above all, the collaboration of outstanding colleagues enabled us to develop numerous valuable and constructive projects and initiatives.

PROJECTS

In the early 1990s, we organized the first Norman Conference on Neonatology, Pediatrics, and Pediatric Nursing, with the aim of fostering closer, more collaborative, and more constructive relationships among the various categories of healthcare professionals. At that time, cooperation among the different disciplines was far from optimal. New technologies, neonatal intensive care, organ transplantation, and many other valuable advances developed within different specialties could be successfully integrated and applied in pediatrics and neonatology.

The event proved highly successful, and its appeal continued to grow from year to year.

INITIATIVES

At that time, the Italian Society of Pediatrics (*Società Italiana di Pediatria*, SIP) encompassed all pediatric specialties, while neonatology and hospital pediatrics were represented by study groups affiliated with the SIP.

For our part, we re-established the hospital pediatrics organization under the name of Italian Society of Hospital Pediatrics (*Società Italiana di Pediatria*

Ospedaliera, SIPO). This was a major milestone and an outstanding success. We organized national and international conferences in Aversa, Montecatini, Capri, Sanremo, Rome, and several other cities.

We also published the Italian Journal of Hospital Pediatrics (*Rivista Italiana di Pediatria Ospedaliera*), which achieved considerable success, largely owing to the active collaboration of colleagues working in hospitals, universities, community healthcare settings, and other areas.

One of our most significant initiatives was the establishment of active collaborations with international scientific societies. This idea took shape during a conference organized by Professor Vassilios Fanos in Cagliari. Following discussions with Professor Murat Yurdakök, we signed a memorandum of understanding between SIPO and the Turkish Pediatric Society.

This marked the beginning of a successful international endeavor that led to the establishment of additional scientific societies: the Italian-Romanian Pediatric Society (IRPS), the Italian-Arab Pediatric Society (IAPS), and the Italian-Albanian Pediatric Society (AIPS).

The establishment of these societies naturally broadened professional collaboration and strengthened international friendships. Subsequently, because of administrative and organizational difficulties within SIPO, “*SIPO nel Mondo*” was founded.

“SIPO NEL MONDO”

“*SIPO nel Mondo*” is a scientific society that offers free membership to all interested professionals. Its members include pediatricians, neonatologists, pediatric nurses, pediatric cardiologists, and specialists from all other fields related to pediatrics and neonatology.

The Society has established its own website, as have the other three scientific societies. To date, these websites have collectively recorded more than 1,300,000 visits.

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LECT 12

MICROBIOTA FROM BIRTH TO WEANING

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The maturation of gut microbiota does not follow a rigid timetable, but shows a continuous change under the influence primarily by milk, complementary foods, antibiotics and the family environment. The gut is colonized mainly during and immediately after birth; there are no convincing evidence that a stable gut microbiota already exists *in utero*. Initially, aerotolerant bacteria such as *Enterobacteriaceae*, *Streptococcus*, and *Staphylococcus* predominate; they consume oxygen and prepare the environment for anaerobic bacteria. Human milk oligosaccharides (HMOs) primarily favour the development of *Bifidobacterium*, particularly those strains capable of utilizing them. These bacteria produce acetate and lactate, reduce intestinal pH and inhibit several pathogens. It is therefore clear that milk not simply “transmits bacteria”, but selects those best suited for the infant gut. Formulas containing HMOs, prebiotics, or synbiotics can induce a similar, but not just the same microbiota of breastfed infants, so that there is no universally optimal formula composition.

Weaning is a genuine biological turning point, not only a nutritional one. During weaning, bacteria capable of breaking down starches, fiber and proteins gradually increase, including *Bacteroidales*, *Lachnospiraceae*, *Ruminococcaceae*, and, later, *Faecalibacterium*. Microbial diversity and the production of short-chain fatty acids – especially butyrate – also increase. Reduction or termination of breastfeeding often appears to produce a more pronounced change than the simple introduction of the first complementary foods. The microbiota gradually shifts from a “milk-oriented” ecosystem to one more similar to that of adults and of the family. For a healthy infant, current evidence primarily supports:

- to continue breastfeeding while complementary foods are introduced, when it is possible and desired;
- to start complementary feeding between 4-6 months of age, according to the infant's capability;
- to gradually offer a diversified diet that includes vegetables, fruits, legumes, grains and other suitable sources of fiber, ensuring adequate iron, energy, and protein intake;
- to avoid ultraprocessed foods and free sugars;
- to discourage any commercial microbiome tests for diet modification or supplement use in a healthy infant;

- to avoid probiotics supplementation without a specific indication or with strains with no documented efficacy.

In summary, the key development is the shift from the idea that the microbiota as a simple list of bacteria to a dynamic ecosystem. Breast milk and HMOs build the *Bifidobacteria*-dominated phase, while dietary variety and the gradual reduction in milk intake drives its metabolic maturation. Associations of microbiota type with allergies, obesity and immune-mediated diseases are intriguing, but at the moment there is no evidence that modifying the microbiota can prevent these conditions.

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LECT 13

ZINC IN NEONATOLOGY: A SMALL TRACE ELEMENT WITH A MAJOR CLINICAL IMPACT

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Zinc is an essential trace element with catalytic, structural and regulatory functions relevant to neonatal growth, immune competence and epithelial integrity and should be considered a key component of neonatal nutrition rather than a minor micronutrient. Healthy term infants generally meet early needs through prenatal stores and highly bioavailable zinc in human milk, so routine supplementation is not indicated. Targeted assessment may be considered in SGA infants with poor growth or additional risk factors, and in infants with impaired linear growth or persistent periorificial or acral dermatitis. Preterm infants are

vulnerable to deficiency because most fetal zinc accretion occurs during the third trimester. Limited stores, rapid growth, immature gastrointestinal function, inadequate intake and increased losses during illness further reduce availability.

Risk rises with parenteral nutrition lacking adequate trace-element provision, delayed enteral feeding, unfortified human milk, malabsorption, and high-output stomas. ESPGHAN recommends a total enteral zinc intake of 2-3 mg/kg/day for preterm infants with a birth weight below 1,800 g [1]. A systematic review suggests that enteral supplementation may reduce mortality, probably improves short-term weight gain and may improve linear growth, but has little or no effect on common morbidities of prematurity. Long-term neurodevelopmental data are lacking [2]. Provision should be individualised according to gestational age, growth, feeding, fortification, gastrointestinal losses and comorbidities. Multicentre studies should determine optimal dosing, validate biomarkers and assess long-term outcomes while monitoring excessive intake and interference with copper metabolism [3].

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LECT 14

INSULIN RESISTANCE: ARE WE LOSING A GENERATION? RECOGNIZE EARLIER. INTERVENE EARLIER. CHANGE THE FUTURE

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Insulin resistance is one of the most important – and most underrecognized – metabolic abnormalities in pediatric medicine. It may develop years before hyperglycemia becomes apparent, while com-

pensatory hyperinsulinemia temporarily maintains normal glucose and HbA1c levels. Consequently, many children may already have significant metabolic dysfunction despite not meeting current diagnostic criteria for prediabetes or type 2 diabetes. Increasing evidence suggests that insulin resistance is a multisystem disorder that contributes not only to obesity and diabetes, but also to metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular disease, chronic kidney disease, and potentially neurocognitive dysfunction [1].

The magnitude of this problem is reaching generational proportions. In 2022, more than 390 million children and adolescents aged 5-19 years were living with overweight, including approximately 160 million with obesity. Pediatric obesity continues to rise worldwide and is accompanied by an increasing prevalence of MASLD and other obesity-related complications [2].

The consequences of youth-onset type 2 diabetes are particularly alarming. Long-term follow-up of the TODAY study demonstrated that by young adulthood, 60.1% of participants had developed at least one diabetes-related complication and 28.4% had developed two or more, highlighting the aggressive nature of metabolic disease when it begins early in life [3].

This presentation proposes a shift from the traditional glucocentric model toward earlier recognition of metabolic dysfunction. The role of insulin resistance in the pathogenesis of obesity, metabolic syndrome, type 2 diabetes, and MASLD will be reviewed, together with the potential clinical value and current limitations of fasting insulin measurements and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Although insulin assays remain insufficiently standardized and universally accepted pediatric cut-off values are lacking, these tools may complement – rather than replace – clinical assessment in identifying children at increased metabolic risk.

The central message is straightforward: if we wait for hyperglycemia before intervening, we may have already lost years of opportunity. The most effective treatment for type 2 diabetes may begin decades before its diagnosis – in the pediatric clinic, within the family, and in the school environment.

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LECT 15

THE FAMILY PEDIATRICIAN AND NEURODEVELOPMENT

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Family Pediatrics in Italy represents a unique, comprehensive care model. From birth to 14/16 years of age care is characterized by its comprehensiveness and continuity. To ensure the protection of the health of all patients, the pediatrician assumes the governance of the care process relating to each patient who has exercised free choice within the doctor-patient trust relationship.

Among the various duties of the Family Pediatrician, specific programs are defined at the regional level aimed at promoting clinical governance, developing proactive care, and caring for patients with chronic conditions.

Neurodevelopmental disorders (NDDs) are a group of complex conditions that begin early in life and typically manifest during the preschool years; such disorders can be considered chronic, a heterogeneous group of conditions that cause difficulties in various aspects of a child's life as they interfere with personal, social, and academic functioning [1]

The scientific literature provides few studies measuring the prevalence of NDDs in the population under the age of 18 according to the DSM-5 (2013) criteria. The following rates have been reported in the most common NDDs: intellectual disability, 0.63%; attention deficit/hyperactivity disorder, 5-11%; autism spectrum disorder, 0.70-3%; specific learning disorder, 3-10%; communication disorders, 1-3.42%; and motor disorders, 0.76-17%. Many studies support the idea that such disorders may be underdiagnosed and that comorbidity of multiple NDDs is the norm [2].

The experience of Family Pediatricians suggests a significant increase in prevalence even in the absence of reliable epidemiological data, with 4% to 12% of patients affected by NDDs with diagnoses confirmed by child and adolescent neuropsychiatry centers.

These figures are likely to be underestimated, given the significant number of patients awaiting diagnosis. Given the high prevalence of NDDs, a specific surveillance project (Longitudinal Assessment of Neurodevelopment) has been launched in the Sardinia Region, involving all Family Pediatricians working in the region. The implementation of this project is primarily based on activities carried out by the Family Pediatrician.

The Childhood Health Project (*Progetto Salute Infanzia*) represents a qualified development of the "age-based health visits" (*bilanci di salute*) programme consisting of a basic plan that includes at least 6 health assessments, among which are the following:

- sensorineural screening (Boel test and Lang stereotest);
- neurodevelopment assessment forms defined by the *Istituto Superiore di Sanità* (ISS).

The neurodevelopment observation and promotion forms approved and shared with the ISS and the scientific societies of pediatrics, neonatology, and child neuropsychiatry represent neurodevelopmental assessment modules to enable the early identification of children with symptoms of NDDs. Each developmental observation and promotion module includes the 6 main behaviors to be assessed to ensure effective neurodevelopmental monitoring of the child in the 3 neurofunctional areas (domains): motor, socio-communicative and regulatory.

Active surveillance by Family Pediatricians and their coordination with specialist Child Neuropsychiatry Units, as well as the definition of Clinical Pathways for NDDs, are essential for early recognition, care, and timely intervention, which are strategic actions for improving the quality of life of people with NDDs.

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LECT 16

NEURODEVELOPMENT AND NEURODEGENERATION: TWO SIDES OF THE SAME COIN?

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Neurodevelopment and neurodegeneration are often viewed as separate areas of neuroscience. Neurodevelopment refers to the processes through which the nervous system is formed, organized, and matured, primarily before birth and throughout childhood and adolescence. Conversely, neurodegeneration describes the progressive loss of neuronal structure and function, usually associated with aging and diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. However, growing scientific evidence suggests that these two processes are closely connected. The way the brain develops can influence its vulnerability to degeneration later in life, while mechanisms involved in early development may become disrupted or reactivated during neurodegenerative disease. Neurodevelopment and neurodegeneration are not simply opposite processes; the former involves growth, organization, and selective elimination, the latter involves dysfunction and progressive loss. Yet both depend on cells' ability to regulate survival, communication, repair, and the removal of damaged components. Genetic factors, brain reserve, synaptic regulation, immune activity, and environmental exposures all provide possible links between early brain development and later neurological decline.

Many genes involved in brain development, including those that regulate synaptic function, protein transport, mitochondrial activity, and cellular repair, may be required both during the formation of neural networks and during their long-term maintenance. The concept of brain reserve also helps explain the relationship between development and degeneration. Brain reserve refers to the brain's capacity to tolerate damage while maintaining normal function. Individuals with greater cognitive or neural reserve may be able to compensate for age-related brain changes for longer periods. Conversely, adverse conditions during development may reduce this reserve, potentially increasing vulnerability to cognitive decline later in life. Synaptic connections provide another important link. Although developmental pruning and degenerative synaptic loss occur at different stages of life, some of the same molecular pathways may be involved. If mechanisms that normally regulate synapse formation and removal become abnormal,

they could contribute to disease processes. The immune system plays an essential role in normal neurodevelopment. Specialized immune cells in the brain, particularly microglia, help shape neural circuits by supporting synaptic remodeling and removing unnecessary cellular material. However, excessive or abnormal immune activity during development can interfere with neural maturation. Later in life, chronic inflammation may contribute to neuronal damage and degeneration. Therefore, the regulation of immune activity is important at both ends of the lifespan. Environmental influences further demonstrate the continuity between development and degeneration. Exposure to pollutants, poor nutrition, chronic stress, or infections during sensitive periods of development may alter brain structure or function. These effects do not necessarily produce immediate neurological disease, but they may influence how the brain responds to future challenges. Similarly, healthy lifestyle factors throughout life may protect neuronal function and reduce some risks associated with cognitive decline. This supports a life-course approach to brain health, in which the foundations of healthy aging are partly established during early development.

In conclusion, neurodevelopment and neurodegeneration are increasingly understood as interconnected processes rather than completely separate events.

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LECT 17

CLIMATE CHANGE AND PAEDIATRIC HEALTH: FROM THE ONE HEALTH APPROACH TO PREVENTION IN THE FIRST 1,000 DAYS

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Climate change represents the true emergency facing humanity, acting as the root cause of many contemporary challenges. As defined by

the United Nations Framework Convention on Climate Change (UNFCCC), it is an alteration of climate attributed directly or indirectly to human activity that alters the composition of the global atmosphere, occurring with extraordinary rapidity and intensity. An enhanced greenhouse effect and anthropogenic sources are responsible for alarming outcomes, including a 1.5°C increase in mean global temperature and elevated atmospheric CO₂ levels compared to the pre-industrial era, manifesting tangibly in heatwaves, floods, droughts, and hurricanes.

Starting from the WHO estimate that approximately 24% of the global disease burden is attributable to environmental factors, and supported by evidence published in *Science* regarding human impacts on global biodiversity, children have a high risk compared to adults [1].

Children breathe more rapidly, inhaling more airborne contaminants per kilogram of body weight. They are more vulnerable to cumulative metabolic harm and possess an immature immune system rendering them susceptible to emerging infections. Lastly, children engage in hand-to-mouth behaviors and active environmental exploration that expose them to soil contaminants, vectors, and pathogens. This process begins even before birth: this is why the One Health approach during the first 1,000 days is paramount, considering the impacts of micro- and nanoplastics during pregnancy and pre-conception endocrine disruptors, which contribute to demographic decline [2]. Beyond emerging zoonoses and spillover events, pediatricians must address heat-related aggression, eco-anxiety, mental health, respiratory risks, allergies, malnutrition, and dehydration driven by climate-induced food insecurity.

Our role as environmental educators must focus on these factors, land pollution, and deforestation. To prevent the burden of past generations from falling on future ones, we must shift paradigms to emphasize that human, animal, and ecosystem health are intrinsically linked, starting with local environmental awareness and sustainable nutrition [3].

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LECT 18

NUTRITION AND ENDOCRINE DISRUPTORS: FROM THE WOMB TO ADOLESCENCE

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Endocrine-disrupting chemicals (EDCs) are exogenous substances capable of interfering with normal hormonal action and, when this interference results in adverse effects, can affect multiple aspects of human health. Exposure occurs through different routes, with diet representing a major source because EDCs may be present in food, water, packaging materials, and food-contact products. Importantly, humans are exposed not to single compounds but to complex mixtures, whose combined effects may be particularly relevant during critical windows of development [1].

The prenatal period represents one of the most vulnerable phases. Maternal exposure to several environmental chemicals, including phthalates, pesticides, polycyclic aromatic hydrocarbons, persistent organic pollutants and metals, has been associated with impaired fetal growth. Studies assessing mixtures of EDCs during pregnancy have reported lower birth weight, slower infant growth and changes in subsequent growth trajectories. Prenatal exposure to persistent chemicals has also been associated with a pattern characterized by smaller size at birth followed by accelerated body mass index gain during childhood, while exposure to widespread chemical mixtures during pregnancy may contribute to an increased metabolic syndrome risk in school-age children [2].

Nutrition remains closely connected to EDC exposure after birth. Breast milk is the optimal source of nutrition for infants due to its nutritional and biologically active components; nevertheless, it may also contain traces of environmental contaminants acquired by the mother. Consequently, breast milk can be considered a biomarker of maternal environmental exposure. Data from the LIFE-MILCH project show the presence of different classes of EDCs in breast milk and associations between some contaminants and maternal dietary patterns. Infant formula and baby foods may represent additional sources of exposure: bisphenols, parabens, phthalates and polycyclic aromatic hydrocarbons have been investigated in infant formulas, whereas trace levels of parabens and their metabolites have been detected in homogenized baby foods [3].

EDC exposure remains relevant during adolescence, another period characterized by profound endocrine and metabolic changes. In Belgian adolescents, mixtures including metals, organochlorine pesticides, PCBs, PFAS, bisphenols and phthalate metabolites were associated with metabolic outcomes, including lipid parameters, BMI z-score and abdominal obesity. More recent evidence indicates that dietary choices, food processing and packaging, and plastic-related behaviors are associated with urinary concentrations of plastic-associated chemicals, while dietary interventions aimed at reducing plastic exposure can modify these levels [4].

Overall, available evidence highlights nutrition as both a potential route of EDC exposure and an opportunity for prevention. Reducing exposure from pregnancy through adolescence, while promoting nutritionally adequate dietary patterns, represents a relevant strategy to protect growth, endocrine function and long-term metabolic health.

ACKNOWLEDGMENT

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LECT 19

THE AMBO PROJECT (ALLIANCE FOR A CHILD-FRIENDLY ENVIRONMENT)

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The nonprofit Association “*Alleanza per un ambiente a misura di bambino*”, hereinafter also referred to as “AMBO” (in English “Alliance for a Child-Friendly Environment”), was formally established under Italian law in December 2025.

So far, 22 Italian scientific societies in the pediatric, neonatology and obstetric-gynecological fields have joined, as well as 50 clinicians and researchers.

The Association was founded on the shared conviction of its Founding Members that climate change and environmental pollution, which are closely interconnected, constitute a public health priority, as repeatedly emphasised by the World Health Organization [1].

The Association pursues the following main objectives:

1. to strengthen cooperation with the relevant public bodies and Ministries involving them in the drafting of joint documents and awareness-raising initiatives;
2. to establish interdisciplinary and multidisciplinary Study Groups, promoting integration with similar initiatives at international level, to prepare scientific documents (e.g. position papers and guidelines), including joint documents involving multiple scientific societies;
3. to analyse issues relating to environmental pollution, endocrine disruptors, climate change, electromagnetic waves and chronic exposure to mobile phones from the earliest years of life, with particular reference to the first thousand days, early childhood, late childhood and adolescence;
4. to promote research and clinical studies on the relationship between the health of children and adolescents and the environment;

5. to promote and implement environmental training programmes for paediatricians, doctors undertaking specialist training and all healthcare professionals, particularly those involved in the care of children and adolescents, through the development of dedicated educational materials;
6. to prepare information and educational materials for families, to be used during routine child health assessments and follow-up appointments, primarily through family paediatricians;
7. to promote educational initiatives in schools in order to raise awareness from an early age of the importance of healthy lifestyles and healthy environments;
8. to develop recommendations aimed at improving the working environment of all healthcare professionals involved in the care of children and adolescents, including for patient education purposes;
9. to develop recommendations aimed at reducing the exposure of women and newborns to harmful substances, particularly endocrine disruptors, in Neonatology, Paediatrics, and Obstetrics and Gynaecology Departments, in view of the particular susceptibility to toxic effects during the first thousand days of life;
10. to prepare information materials on health and the environment to be made available through the Association's official website and the websites of AMBO members, for both healthcare professionals and families.

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LECT 20

THE ROLE OF ENVIRONMENTAL MEDICINE: THE ONE HEALTH APPROACH

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“One Health” is a strategic, systemic, and integrated approach to health, based on the recognition that human well-being is closely linked to the health of animals and the environment in which both live. This approach is officially recognized by major national and international organizations such as the World Health Organization (WHO),

the Food and Agriculture Organization (FAO), the World Organisation for Animal Health (WOAH/OIE), the Italian Ministry of Health, and the European Commission. One Health promotes multidisciplinary collaboration among physicians, veterinarians, epidemiologists, biologists, ecologists, agronomists, sociologists, economists, and policymakers to prevent and manage health emergencies, with a particular focus on emerging infectious diseases, food safety, antimicrobial resistance, and environmental changes. The One Health concept is deeply intertwined with the Sustainable Development Goals (SDGs) outlined in the United Nations 2030 Agenda, representing a strategic cross-cutting approach to achieving lasting global well-being. Among the most relevant goals where One Health finds full application are Goal 3 (Good Health and Well-being) and Goal 15 (Life on Land).

The concept of One Health originates precisely from the integration of human health, animal health, and environmental health, recognizing that the health of each element is intrinsically interconnected. The health dimensions – human, animal, and environmental – are deeply interdependent. They cannot be analyzed or addressed separately:

- pathogenic agents causing zoonoses (diseases transmitted from animals to humans) account for over 70% of new emerging infections;
- the environment acts as a vector and reservoir for infectious agents, as well as a mediator of toxic substances and climate changes that influence disease spread;
- any imbalance in one of these three domains produces cascading effects on the others. A key example is deforestation, which reduces biodiversity, alters natural habitats, and increases contact between wild animals and humans, facilitating pathogen species jumps.

Biodiversity represents the invisible and fundamental pillar supporting ecosystem stability and, consequently, our global health. The variety and richness of animal, plant, and microbial species in a natural environment ensure a dynamic equilibrium that contributes to regulating vital processes such as nutrient cycling, air and water quality, and pathogen regulation. Furthermore, dangerous anthropogenic practices, such as illegal wildlife trade, uncontrolled hunting, and encroachment into natural habitats, foster direct and close contact among wild, domestic, and human populations.

Protecting biodiversity is therefore not merely an ecological concern, but a strategic priority for

pandemic prevention, food security, and planet sustainability.

The One Health approach is critical to effectively combating antimicrobial resistance, as it fosters integration and cooperation across human medicine, veterinary medicine, and environmental sciences.

One Health is not merely a public health strategy; it represents a cultural shift capable of bridging the traditional view separating human, animal, and environmental health in a holistic and new epigenetic perspective.

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LECT 21

A HEALTHY DIET FOR A HEALTHY CHILD: FAMILY AND SOCIAL MEDIA BETWEEN RISKS AND OPPORTUNITIES

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The recent UNICEF report *Feeding Profit: How Food Environments are Failing Children*, drawing on nutritional status data with near-global coverage, has shown that, for the first time, obesity prevalence in school-age children and adolescents has overtaken that of underweight, marking a global epidemiological shift [1]. Such a rapid increase cannot be explained by genetic changes, which occur over much longer timescales, but is most likely the result of the impact of an obesogenic environment. Indeed, sugary drinks and sweet and salty snacks are now easily accessible and, above all, subject to aggressive marketing, resulting in nutrient-poor, energy-dense diets that contribute to weight gain. Adding to this alarming picture, in 2023 more than one-fifth of the child and adolescent population presented with an eating disorder [2]. It is therefore essential to focus on the earliest origins of eating behavior: the family. Food preferences are in fact formed early in life, primarily through parents, both through direct influence, such as control over food availability and taste education, and indirect influence, such as modeling. To this are added several key determinants, some more recent, such as social media, and others already well established, such as socioeconomic context. Indeed, children

and adolescents' rising exposure to social media introduces conflicting cues around body image and food, contributing to distorted perceptions and unhealthy habits [2]. Furthermore, digital environments are also emerging as an increasing source of information for parents regarding their children's health and nutrition [3]. Therefore, in an increasingly complex context, promoting healthy eating habits from early childhood is essential, with responsive parenting style and adequate nutritional literacy representing the pillars on which to build effective prevention [2].

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LECT 22

THE ROLE OF COMMUNICATION

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The postpartum period represents a phase of extreme vulnerability for new mothers, during which professional support is widely regarded as a cornerstone of parental confidence, particularly with respect to breastfeeding and infant care [1]. However, this need is very often unmet by traditional channels, which likely favors the use of social media as a source of support and information [1, 2]. The scale of social media adoption today, spanning billions of users globally and tens of millions within Italy alone, has reshaped how health information circulates, shifting the paradigm away from one-directional, expert-driven messaging toward a dynamic, participatory exchange. While this fosters trust, perceived closeness, and wider dissemination of health messages, it also exposes users to the risk of misinformation, amplified by platform algorithms designed to reward interaction rather than factual reliability, and by perceived credibility that is often disconnected from actual competence. In the pediatric field, this risk is amplified, as online messages influence parental decisions regarding

breastfeeding, nutrition, and vaccinations, within a digital landscape where board-certified pediatricians remain a small minority among those producing health-related content online [2, 3]. To help bridge this gap, the Italian Society of Pediatrics (*Società Italiana di Pediatria*, SIP) piloted a hands-on initiative involving a cohort of pediatrician-influencers, tasked with sharing the society's official content across their own channels. Over the twelve-month pilot period, the page's audience growth, user interaction, and content visibility all rose markedly, and organic exposure to individual posts improved as well; participating pediatricians largely described the experience in favorable terms [3]. These findings suggest that, since families will seek support online regardless, the active and qualified presence of healthcare professionals in the digital space, particularly during the delicate postpartum

and early childhood period, represents an effective strategy for guiding mothers toward reliable sources and countering misinformation. This strategy, however, cannot be separated from a strengthening of primary pediatric care, with particular attention to supporting maternal emotional well-being [1-3].

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