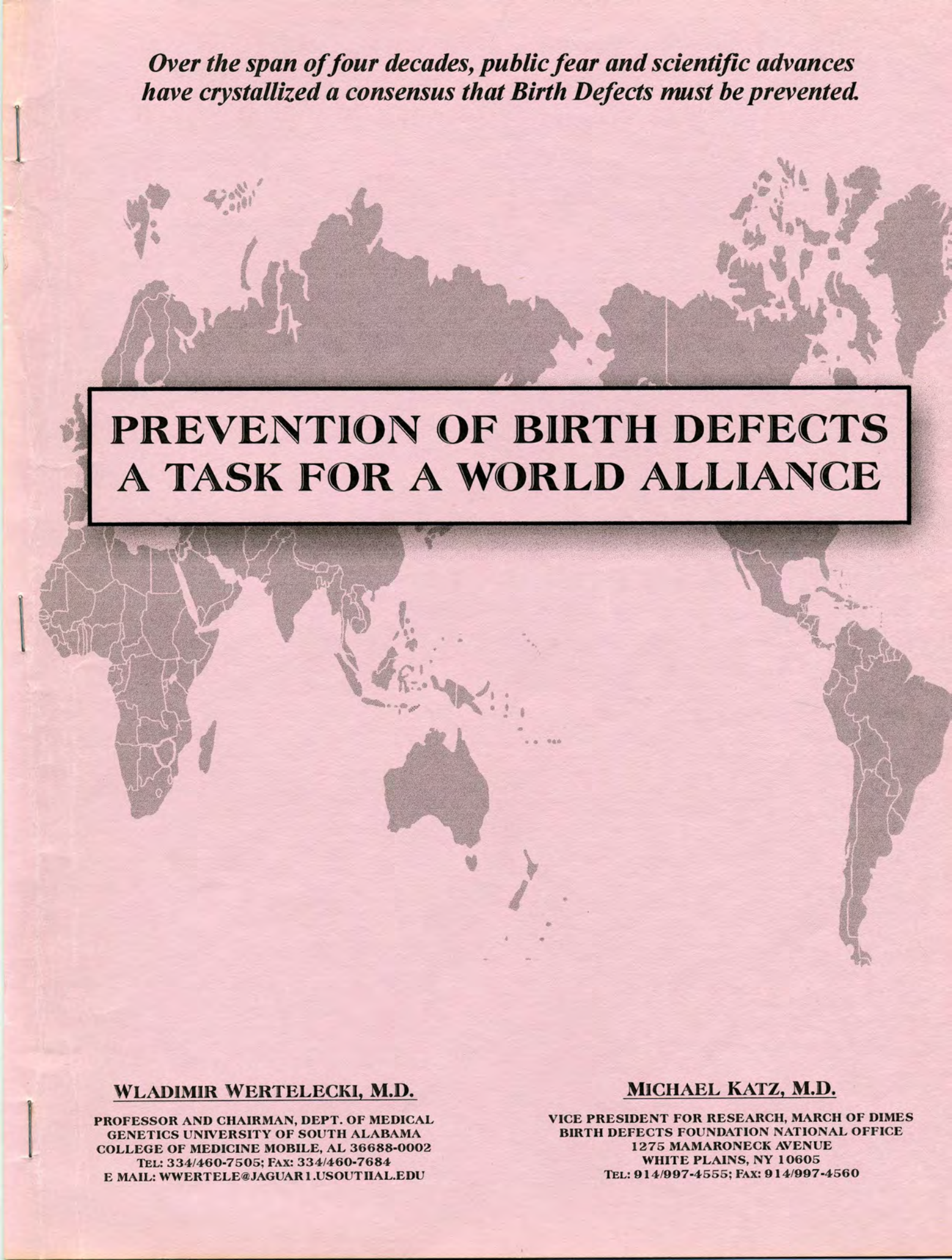


*Over the span of four decades, public fear and scientific advances have crystallized a consensus that Birth Defects must be prevented.*



## **PREVENTION OF BIRTH DEFECTS A TASK FOR A WORLD ALLIANCE**

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*Participants of the World Alliance of Organizations for the Prevention of Birth Defects first meeting held January 1618, 1995, in the castle "De Hooge Vuursche" and the City Hall of the Hague. From left to right (seated) are Drs. W. Wertelecki, M. Katz, O. Mutchnick, Mrs. I. Roelefsz, I. Nippert, (standing) V. B. Penchaszadeh, B. J. Botting, Paul Peters, and Y. S. Poortman. (Other participants are not shown.)*

Versions of this paper have appeared in Chinese, English, Spanish, Russian and Ukrainian (Acta Paed. Sin. Vol. 37 No. 3 1996; Jpn. J. Hum. Genet. 40:295, 1995; Medico Interamericano 5:185, 1995; Ruskyj Vestnyk Perinatologia Pediatrii; J. Ukrainian Med. Assn. 42:137, 1996).

# PREVENTION OF BIRTH DEFECTS A TASK FOR A WORLD ALLIANCE

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*"... it must be realized that congenital malformations are manifestations of prenatal pathology, an area as large and complex as that of postnatal pathology ... obscured by the inaccessibility of the unborn ... and unresponsive to investigative methods traditional in postnatal research..."<sup>(1)</sup>*

*Josef Warkany, M.D.*

We are pleased to report the formation of the World Alliance of Organizations for the Prevention of Birth Defects (WAPBD). In this context we wish to recognize the achievements of pioneers in teratology and medical genetics who have advocated the prevention of birth defects (BD) which is reflected in the attached bibliography. In particular, we single out Dr. Josef Warkany, who was one of the founders of experimental teratology.

In 1957, after an effective vaccine was developed, he suggested changing the target of the March of Dimes National Foundation of Infantile Paralysis from poliomyelitis to congenital malformations and said, "... Our plans for patient care and research were written in the Office of Franklin Delano Roosevelt, which was maintained in its original form by Mr. Basil O'Connor, then President of the Foundation".<sup>(1)</sup> (Figure) In 1960, Warkany with Drs. Clarke Fraser and Jim Wilson promoted the creation of the American Teratology Society and became its first President. In 1986, Dr. Warkany received the first Basil O'Connor Award and recalled how nearly 30 years earlier his suggestions to foster genetic counseling were met with a "stonewall of opposition".<sup>(2)</sup> Since his death in 1992, the American Teratology Society has sponsored an annual Warkany Memorial Lecture.

The WAPBD was organized at a meeting convened by the March of Dimes Birth Defects Foundation in New York on April 3-5, 1994, and was incorporated six months later. Present were representatives of organizations comprising health care workers, scientists, and, most important, concerned public, such as affected individuals and their families. Following the incorporation, a Board of Directors was elected, and a meeting was held on January 17, 1995 in The Hague, The Netherlands (see rear flyleaf). The



*Mr. Basil O'Connor (left), President of the then March of Dimes National Foundation of Infant Paralysis discusses plans to establish a national program for the study of congenital malformations with Dr. Josef Warkany. Prestigious yearly events to honor those of greatest achievement in the study of congenital malformations carry now the names of O'Connor and Warkany.*

WAPBD will hold its inaugural meeting in conjunction with the 27th Annual Meeting of the European Society of Human Genetics and the 7th Annual Meeting of the Society of Human Genetics in Berlin on May 23-27, 1995. In 1996, the WAPBD will meet in conjunction with the Quinquennial Congress of the International Society of Genetics and Human Genetics to be held in Rio de Janeiro, Brazil and in 1997, the meeting still to be scheduled will be held in Asia, Africa, Australia, or Eastern Europe (see Addendum).

A birth defect, as defined by the WAPBD, is "any anomaly - functional or structural - that presents in infancy

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or later in life and is caused by events preceding birth, whether inherited, or acquired." This definition includes structural malformations and functional deficits, in particular mental retardation. The WAPBD considers that "the impact of birth defects transcends cultural, ethnic, socio-economic, and political boundaries ...". The WAPBD is "dedicated to the prevention, cure, and amelioration of birth defects by the application of the existing knowledge; it recognizes the need for new knowledge that derives from vigorous scientific research programs; it seeks to decrease the gap between new scientific discoveries and their practical application in health care and prevention; it underscores the need for health care providers to have prompt access to up-to-date knowledge about causes and methods of prevention and that prevention must be accessible to all segments of a population." Furthermore, the WAPBD calls for "birth defects prevention to become an integral part of all health care systems; to provide access for parents to accurate unbiased information to enable them to make decisions that they consider appropriate." The WAPBD has issued a statement of principles shown in Table I.

Birth defects remain a leading cause of infant mortality and in spite of the broad scientific advances their burden on society has not diminished (Table II). New ideas and approaches are required. Moreover, prevention of birth defects depends on an interaction among multiple scientific disciplines and public political bodies. Therefore, WAPBD will advocate integration of genetics, teratology, epidemiology, health care delivery systems and public education.

Traditionally, exploration of causes (etiology) and mechanisms (pathogenesis) has been the basis on which prevention is developed. Such an approach, when successful, can result in direct prevention through the

avoidance or elimination of causes or the interruption of sequential events. In this regard, the use of iodized salt to eliminate endemic goiter and cretinism, rubella vaccination to prevent rubella syndrome and the testing of drugs to prevent their teratogenic effects are victories of direct prevention. These achievements have led to the establishment of information systems about teratogens.<sup>(3-5)</sup> Genetic counseling, based on prognosis of reproductive risks, prognosis has been made available to a growing proportion of prospective parents. Under ideal circumstances, this allows for primary prevention through a redirection of behavior. Examples of this approach abound. Women contemplating pregnancy can be cautioned against the use of certain legitimate drugs, such as anticonvulsants and masculinizing hormones. They can be cautioned against consumption of alcohol, of illicit recreational drugs, smoking and exposure to radiation. They can be encouraged to consume folic acid. Women beyond 35 years of age, who are at a greater risk for bearing children with trisomies can be given specific guidance. Effectiveness of genetic counseling to enhance health care systems and present birth defects remains an active area of research.

In contrast to direct prevention, indirect prevention is possible before we understand etiology or pathogenesis. For example, before the etiology or treatment of tuberculosis or leprosy were understood and treatment became available these disorders were rapidly declining in industrialized societies as a result of better living conditions.<sup>(6-8)</sup> Another example of indirect prevention is illustrated by the use of aspirin which lowers the risks of development of pre-eclampsia, intrauterine growth retardation, alcohol induced malformations (in mice) and human colon cancer, but the mechanism of tumor effects is unknown.<sup>(9-13)</sup>

**Table I. Statement of Principles by the "World Alliance of Organizations for the Prevention of Birth Defects, Inc."**

The Alliance will promote:

- Respect for persons with disabilities.
- Protection from stigmatization of and discrimination against those affected with birth defects, as well as those at risk for transmission of birth defects to their children.
- Dissemination of knowledge about prevention to prospective parents.
- Primary prevention, as the most important means.
- Commitment of all countries through public policy to the prevention of birth defects.
- Universal access to preventive, therapeutic and psycho-social services.
- Dedication of a proportion of every health budget to the prevention of birth defects.
- Incorporation of prevention as a routine component of health care systems.
- Involvement of a wide range of health professionals.
- Collaboration of experts for the purposes of expansion of research and surveillance.
- Involvement of lay interested parties, families, volunteers and others in the cause of prevention.
- Education of the professionals and the public.
- International communication and sharing of information.

The unique challenges posed by birth defects are underscored by their high prevalence which may imply that "in the world of early embryos, malformations may be the norm".<sup>(14)</sup> Many studies have shown the massive impact of congenital malformations upon the development of primate embryos.<sup>(15-20)</sup> It is estimated that 15% of recognized human pregnancies end in spontaneous abortion and that over 60% of aborted early human conceptuses have structural abnormalities.<sup>(14)</sup> It has also been calculated that without spontaneous abortions, the observed rate of 2-3% of congenitally malformed newborns would increase to approximately 12%.<sup>(8)</sup> Some investigators believe that prenatal pregnancy losses are not random but represent a natural screening process.<sup>(21-23,14)</sup> It has been suspected that advancing maternal age alters or "relaxes" this selective mechanism, which may explain the excess of Down syndrome among the offspring of older mothers regardless of whether the chromosomal non-dysjunction is of maternal or paternal origin.<sup>(24-25)</sup> According to some studies it may be possible to heighten the efficiency of prenatal selection against the fetus with birth defects.<sup>(26)</sup> This concept is embodied in the term "terathanasia", coined by Warkany to denote "... the process of spontaneous removal by prenatal death of malformed conceptuses ... this process can be supported ... In contrast to induced abortion of defective embryos, supportive terathanasia aims at reinforcing conditions that naturally eliminate abnormal conceptuses ...".<sup>(8)</sup> Concurrently, Warkany also stressed that "terathanasia should not be thought of as a final method for prevention ... (which remains) the avoidance or removal of causes."<sup>(6)</sup>

A recent triumph of indirect prevention concerns the discovery that small amounts of folic acid can prevent the majority of occurrences of neural tube defects (Statement "Preventing Spina Bifida and Other Neural Tube Defects" from Centers for Disease Control and Prevention, Birth Defects and Genetic Disease Branch, August 1993). Following the initial reports suggesting that periconceptional vitamins prevented NTD, this effect has been later confirmed by several strictly conducted epidemiologic investigations.<sup>(27-32)</sup> In August 1993, the USA Centers for Disease Control and Prevention have declared that a daily consumption of 0.4 mg of folic acid by women of child-bearing age can prevent 50-70% of all cases of neural tube defects. Moreover, other investigators have broadened this view by proposing that multivitamin supplementation (including 0.8 mg of folic acid) may decrease the prevalence of other congenital anomalies.<sup>(33)</sup>

Other forms of prevention, include those that provide a rationale for the screening and treatment of inborn errors in the newborns and for early intervention in utero. Early remediation strategies for children with disabilities and mental retardation can also be effective in ameliorating the conditions that afflict them.<sup>(34-40)</sup>

Prevention programs are greatly facilitated by investments in data collection and reporting of their effects. Since the thalidomide tragedy, birth defects surveillance has been established in many countries.<sup>(41)</sup> The purpose of

**Table II. Birth Defects Among Pediatric Hospital Admissions** <sup>(56-57)</sup>

| Category and number of admissions<br>(number of admissions) | Seattle | Caracas |
|-------------------------------------------------------------|---------|---------|
|                                                             |         |         |
| Total                                                       | 4115    | 6161    |
| Neoplasias                                                  | 230     | --      |
| Heart Malformations                                         | 162     | 38      |
| Genito-urinary Malformations                                | 159     | 18      |
| Seizures                                                    | 137     | 12      |
| Cerebral Palsy                                              | 99      | --      |
| Sickle Cell Anemia                                          | 23      | 78      |
| Juvenile Diabetes                                           | 61      | 10      |
| Facial Clefts                                               | 51      | 9       |
| Meningomyelocele                                            | 44      | 6       |
| Pyloric Stenosis                                            | 14      | 36      |
| Cryptorchidism                                              | 10      | 30      |
| Scoliosis                                                   | 26      | --      |
| Down syndrome                                               | 25      | --      |
| Mental Retardation                                          | 24      | 13      |
| Limb Malformations                                          | 23      | 5       |
| Cystic Fibrosis                                             | 23      | --      |
| Collagen Disorders                                          | 19      | --      |
| Skeletal Malformations                                      | 18      | --      |
| Skin Angiomas                                               | 18      | --      |
| Hydrocephalus                                               | 18      | 8       |
| Hirschsprung Disease                                        | 15      | 5       |
| Multiple Congenital Anomalies                               | 10      | 14      |
| Hypospadias                                                 | 10      | 14      |
| Hemophilia                                                  | 10      | 11      |
| Imperforate Anus                                            | 10      | 8       |
| Neurofibromatosis                                           | 9       | --      |
| Admissions (%)                                              |         |         |
| Genetic Disorders                                           | 4.5 (1) |         |
| Polygenic Disorders                                         | 22.1    |         |
| Developmental Anomalies                                     | 13.6    |         |
| Familial Disorders                                          | 13.0    |         |
| More than 20 Admissions                                     |         |         |
| Genetic Disorders                                           | 13.0    |         |
| Overall                                                     | 1.2     |         |

(1) In Caracas the figure was 3.9%

such monitoring is to note as early as possible potential new teratogens or mutagens being introduced into the environment. Birth defects monitoring relies on direct data collection strategies.<sup>(42-44)</sup> However, less direct approaches are also needed, particularly to grasp complex issues such as those posed by mental retardation and illustrated in Table III.<sup>(45)</sup>

Policies and their rationale for the prevention of birth defects have been formulated for some time.<sup>(45-55)</sup> The magnitude of the challenge justifies a World Alliance of Organizations for the Prevention Birth Defects.

**Table III. Measuring Effects of Prevention Programs in Mental Retardation.**

Selection of data pointers from 43 indices.<sup>(45)</sup>

- Utilization of Family Planning Facilities.
- Genetic Counseling Services.
- Genetic Carrier Testing.
- Prenatal Care in Public Programs.
- Women Receiving Adequate Prenatal Care.
- Use of Maternal Serum Alpha-Fetoprotein Assay.
- Amniocentesis for Women 35 Years of Age or Older.
- Teenage Births/Teenage Fertility Rates.
- Out-of-Wedlock Birth Rates.
- Alcohol Usage and Alcoholism Treatment Data.
- Accuracy of Birth Certificates.
- Birth Defects Reported.
- Newborn Screening for Metabolic Diseases.
- Tracking Systems for High-Risk Infants.
- Neonatal, Infant Mortality Rates.
- Early Intervention Programs.
- Immunization Levels.
- Presence of Family Support Services.
- Education Programs for Service Providers.
- Use of Family Life Curriculae in School.
- Education of the Public.

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## ADDENDUM

THE BOARD OF DIRECTORS OF THE ALLIANCE ARE: BEVERLEY BOTTING, ANDREW CZEIZEL, MICHAEL KATZ, PIERPAOLO MASTROIACOVO, OSVALDO MUTCHINICK, IRMGARD NIPPERT, VICTOR PENCHASZADEH, YSBRAND POORTMAN, WLADIMIR WERTELECKI. THE OFFICERS OF THE ALLIANCE ARE MICHAEL KATZ (PRESIDENT), YSBRAND POORTMAN (VICE-PRESIDENT) AND WLADIMIR WERTELECKI (SECRETARY-TREASURER).

THE WORLD ALLIANCE OF THE ORGANIZATIONS FOR THE PREVENTION OF BIRTH DEFECTS, INC. INVITES ALL ORGANIZATIONS AND INTERESTED INDIVIDUALS SUPPORTING OUR AIMS TO JOIN US.

FOR ADDITIONAL INFORMATION ABOUT THE ALLIANCE, PLEASE CONTACT ONE OF THE OFFICERS LISTED ON PAGE ONE.

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