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Proceedings of the Second International Conference on Neural Tube Defects

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This is a review of the proceedings of the Second International Conference on Neural Tube Defects. This was an interdisciplinary meeting with the common emphasis on neural tube defects research. The various presentations from this 3½–day meeting are summarized. ***Genet Med* 2003:5(5):400–406.**

The second international conference on neural tube defects convened from May 4 to 7, 2002. All topics that were discussed concerned different aspects of neural tube defects, such as embryology, suspected teratogenic factors, candidate genes, mouse models, epidemiology, and of course, folate, both in terms of experience with population supplementation and mechanisms by which folate exerts its protective effect. The origin of this meeting was based on discussions following a workshop on current research in neural tube defects at the American Society of Human Genetics in 1994. The consensus after the workshop was that the individuals involved in neural tube defect research could benefit from such a conference so that collaborations and exchange of ideas could expedite future research. The first meeting, with close to 40 attendees, convened in 1999 in conjunction with the David W. Smith Meeting on Malformations and Morphogenesis in Schlangenbad, Germany. The second meeting in 2002 at Seabrook Island, South Carolina, had 70 attendees from ten countries. Pre- and postdoctoral students were active participants and had the opportunity to interact with researchers from around the world. It is becoming clear that such a format can be a great forum for exchanging ideas and developing ideas for research projects. Summaries of the various topics that were covered are presented in this report.

EMBRYOLOGY

Three presentations covered the embryology of neural tube defect (NTD). Dr. Muriel Harris described neural tube closure in the mouse. The mouse has three closure sites, with the site of closure 2 (that between the hindbrain and midface) varying in position. Failure of closure 2 results in exencephaly, failure of closure 3 causes "split face," and failure of closure 1 causes spina bifida. In addition, these different zones of closure in the mouse are dependent on different genes, and the resultant mouse mutants have specific anomalies, an example being that some mouse mutants only have exencephaly, whereas others only have rachischisis, etc. This suggests that the mechanisms among sites must therefore be different, and experimental or study design must incorporate this fact.

Comments after the presentation, however, suggested that the mouse may not be a good model for human neural tube defects because the human apparently has only two closure sites, and the mechanisms of closure within some or all zones may be different than in the mouse.

Dr. Henny vanStraaten presented an interesting analysis of the role of actin in neural tube closure in the chick. He described how closure normally begins in the mesencephalic level, then proceeds in phases, with groove formation, groove deepening, lumen extension, and lumen widening occurring in subsequent steps. Because actin is found in the mesencephalic region, it was hypothesized that it may be involved in closure, and indeed, actin distribution is heaviest in areas where closure begins, but is also found in other areas of the neural plate. Furthermore, cytochalasin D, a substance that causes depolymerization of actin, causes cessation of neural tube closure, and actually leads to unrolling of the previously formed neural groove. Dr. vanStraaten also suggested that the neural tube closes in a button fashion, rather than in a zipper fashion, which could be the explanation of thoracic level only defects. Dr. Sadler commented that other mesenchymal factors besides actin are important in neural tube closure, and the relative role of each varies among species.

Dr. Jeffrey Golden gave a keynote talk on patterning of the dorsal neural tube, and reviewed the role of both transcription and secreted factors in neural tube closure. Dr. Andrew Copp also reviewed mechanisms of neural tube closure, but from a slightly different perspective. In the mouse, closure begins at Day 8.5 and proceeds until Day 10.5, with anterior closure more complex than posterior. There are three modes to closure, with the first being the formation of a median hinge point by the straight neural folds coming together. This is followed by the formation of dorsal bending points at the edges of the neural folds, with the midline bend then being lost and assuming a more rounded shape. Genes involved in this process are multiple, with sonic hedgehog (SHH) being strongest during the first phase, and probably related to notochordal influence of the formation of the midline hinge point. However, it is clear

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that SHH is not the only notochordal factor involved in this process. Conversely, BMPs and WNT may be involved in the dorsolateral bending of the neural tube, and experiments are in progress to explore this further.

EPIDEMIOLOGY

Neural tube defects are heterogeneous, as shown by presentations given by Drs. Mary Sellers and Laurie Seaver. Dr. Seller presented a detailed review of her study of human embryos with neural tube defects. She noted differences in sex ratios in fetuses with neural tube defects at different levels. Whereas the M/F ratio is < 1 for anterior neural tube defects (as well as for lumbar spina bifida), the ratio is 1.63 for lumbosacral spina bifida and 1.60 for sacral spina bifida. In the embryos with chromosome anomalies and neural tube defects, most were low lumbosacral (22/26), whereas the other 4 were anencephaly or encephalocele. In none was the thorax involved. Finally, embryos with iniencephaly had other anomalies in 100% whereas only 4% of those with lumbosacral or sacral spina bifida had other anomalies. The distribution of these other anomalies was nonrandom, and appeared to be causally related to the site of the lesion (e.g., cardiac defects and thoracic level spina bifida; renal defects and thoracolumbar defects).

Dr. Seaver presented her studies on human fetuses with neural tube defects with regard to the frequency of other anomalies. In general, 16% have other anomalies, with 46% of those having recognizable syndromes and associations. Heart defects and clefts are most common, followed by other midline anomalies and limb defects. Some of these anomalies could be potentially explained by mechanistic factors, such as a short spine causing a short trunk which in turn would lead to the occurrence of omphalocele or diaphragmatic hernia. Interestingly, the rate of neural tube defects with other anomalies is declining more slowly than other neural tube defects.

These careful phenotypic characterizations underscore the diversity of mechanisms involved in NTD development and highlight the importance of documenting the phenotype to insure appropriate genotype/phenotype correlations.

TERATOGENS

Talks in this group focused on various agents (besides folate deficiency) that could cause NTDs, and the potential mechanism by which these teratogens could act.

Fumonisin

Dr. Janee Gelineau-vanWaes and Dr. Tom Sadler presented their work with fumonisin, a corn fungus. Dr. Gelineau-vanWaes reviewed the epidemiologic findings of high rates of human neural tube defects in areas with high levels of fumonisin B1 in corn. Fumonisin B1 is a fungus that can be a contaminant of food products derived from corn and other grains. Dr. Gelineau-vanWaes described studies with mouse models, particularly the LMBc strain, which has increased sensitivity to pharmacological compounds. Administration of fumonisin B1 caused 79% of the offspring to have neural tube defects. The mode of action was thought to be the inhibition of ceramide synthase, which leads to ganglioside depletion, decreased folate uptake, and the resultant neural tube defect. It was noteworthy that coadministration of GM1 rescued the phenotype, supporting the notion that ganglioside depletion was key. Dr. Sadler also described his work with fumonisin, but used it to study the potential effect folate deficiency has on the development of neural tube defects. Using mouse whole embryo cultures, he essentially found that folic acid deficiency primed the embryo for additional insults (e.g., hyperthermia), because the presence of folate decreased the amount of cell death, particularly in neural crest cells.

Obesity

Taking a slightly different approach, Margaret Watkins described the epidemiologic studies that address the possible correlation between obesity and neural tube defects in humans. In general, it has been found by several studies that obese females have at lease a 2-fold increased risk for neural tube defects. This translates into 8% to 16% of the neural tube defects being caused by maternal obesity. Possible mechanisms include hyperinsulinemia/diabetes predisposition, endogenous estrogen, hypoxia, abnormal nutrition, dietary behavior, or unmet nutrient requirement among obese females. It was questioned whether the increasing obesity rate may be offsetting the expected decline in neural tube defects postfortification.

MOUSE MODELS

Mouse models of NTD provide an important resource for characterizing genes that influence neural tube closure, allowing the potential for identifying candidate genes for human studies. Several mouse models of neural tube defects have been studied, and this was the subject of a number of presentations (see Table 1 for a summary of mouse models discussed). Dr. Claudia Kappen reviewed her work with the Isl-1 mouse. In mouse models in which there is overexpression of Isl-1, there is a variety of defects ranging from lumbosacral dysgenesis to sirenomelia. The notochord is present in these mice, but the presumptive mechanism is increased cell death. This mouse model is considered to be a good model for diabetes-associated neural tube defects. Dr. Philip Stanier described his work with the looptail mouse, in which closure 1 is abnormal. Looptail fetuses with homozygous mutations have a phenotype similar to human rachischisis, whereas heterozygotes have tail defects, as well as head wobbling, open eyelids, heart defects, and imperforate vagina. The wild type product of looptail is thought to be involved in protein-protein interaction, particularly during gastrulation. It is noteworthy that looptail protein is expressed in the developing neural tube but with the exclusion of the floor plate. Dr. Nicholas Green provided a review of his work with the Cited2 mouse mutation. The Cited2 gene is expressed in the mid and hindbrain neural crest. Homozygous mutations are lethal, with the embryos having heart and neural tube defects. Cell death is increased before closure of the neural

Table 1
Mouse models

Mouse model	Genetics	Phenotype	Folate-responsive?	Scientist
Isl-1	?	Lumbosacral dysgenesis, sirenomelia	No	Claudia Kappen
Looptail	Semidominant	Homozygous-rachischisis, Heterozygous tail defects, open eyelids, heart defects	Unknown	Phillip Stanier
Cited 2	AR	Homozygous-lethal, with heart and neural tube defects	Yes	Nicholas Green
Curly tail	AR	Exencephaly, spina bifida cystica, +/− curly tail	No	Madelyn Brouns, Patricia Cogram
Crooked tail	AR	Exencephaly	Yes	Elizabeth Ross
Bent tail	X-linked deletion	Exencephaly	Unknown	Barbara Franke

tube, whereas patterning is apparently unaffected. Folic acid supplementation prevents neural tube defects in the Cited2 mouse, although apparently not by inhibition of apoptosis. Drs. Patricia Cogram and Madelyn Brouns both spoke about the curly tail mouse model. The curly tail gene mutation, when homozygous, causes neural tube defects, including exencephaly, spina bifida, and most often, curly tail. The penetrance is reduced, and expression in part depends on genetic background. This mutation is resistant to folic acid supplementation. It is thought that the normal relationship between growth, curvature, and closure of the posterior neuropore is disrupted in this mouse. This is related to dorsoventral cell proliferation imbalance, with a temporarily increased ventral curvature, which in turn generates a mechanical stress that causes delayed closure of the posterior neuropore and spina bifida. However, the identity of the gene is unknown, and Dr. Brouns reviewed her work seeking to identify the gene that is responsible for the curly tail phenotype. The gene has been mapped to a fairly small region, with a few candidate genes in the region being investigated.

Dr. Cogram also described her work on the curly tail mouse, but in a different arena. The curly tail mouse, although folate resistant, is inositol responsive. The D-chiro form of inositol is more effective that the myo form for reducing NTD frequency. The question that Dr. Cogram was attempting to answer is the mechanism through which inositol exerts its protective effect. She has found that inositol stimulates protein kinase C, which is involved in the normalization of posterior neuropore closure, with particular isoforms more likely to mediate the effect of inositol than are others.

Dr. Elizabeth Ross presented her work on the crooked tail mouse, which is a folate-sensitive mouse model. In homozygous mutants, there is thinning of the medial hinge region. Based on her research using various dietary supplements, including folic acid, she has concluded that dietary folic acid alters red blood cell folate levels, but not weight gain or fertility. Folic acid preferentially rescues female embryos, so the gender skew that had previously been observed in curly tail mice is eliminated. The homocysteine levels are the same in homozygotes as in heterozygotes, and paradoxically, the homocysteine levels went up with increasing levels of folic acid. The questions that arise include whether lethal defects are shifted to viable, but impaired individuals, and whether some individuals would be better served by some other supplement as well.

Dr. Barbara Franke described work with different mouse strains, with an emphasis on the molecular basis of the effect of nutrients in the etiology of NTD. Because zinc is one of the nutrients whose deficiency is associated with neural tube defects, she looked at the Bent tail mouse, which has a deletion that includes the *zic3* gene. She found that 11% have exencephaly, with hind and midbrain closure defects most common. She had postulated that *Zic3* was likely the causative gene for human X-linked neural tube defects, but cited a paper that did not find *zic3* mutations in 3 multicase families.

However, other *zic* genes in mice have also been shown to cause neural tube defects, with *zic1* and *zic2* knockouts both associated with neural tube defects. She also presented work on the curly tail mouse, which is folate resistant but inositol responsive. Genes in the myoinositol pathway were examined, and whereas two were not found to be associated with neural tube defects, the third, AP-2, may be occasionally involved in neural tube defect occurrence in humans. Finally, she described initial work using a microarray, in which 120 to 130 genes involved in the folate or inositol pathway are arranged. This experiment is in process.

CANDIDATE GENES, MOUSE, AND HUMAN STUDIES

Adrianne Joo from Dr. Andrew Spicer's lab examined the various hyaluronan (HA) synthases. The premise of this research is that hyaluronan is important in cell migration, tissue volume changes, cell proliferation, and matrix organization. It is important for creating cell-free areas into which cells migrate, and because neural crest cells are a type that migrate into cell free areas, it would be logical to look at hyaluronan synthase as a possible candidate gene. HA synthase occurs in three forms, with HAS 2 being the dominant form in the embryo. HAS 2 knockout mice have growth retardation, lack of endocardial cushions, vasculogenesis defects, and variable neural tube defects.

Rolf Stottman from Dr. John Klingensmith's laboratory described his work on BMP (bone morphogenetic protein) signaling in mice, which is relevant to many embryonic patterning events. BMPs and BMP targets are expressed in the neural tube, and BMP 5/7 double mutants have neural tube defects. One antagonist of BMP is noggin, and ablation of noggin leads to anencephaly, as well as other neural tube defects. Noggin mutants have abnormal neural crest, and there may be a failure of dorsolateral hinge points. There also appears to be a difference in expression depending on the genetic background.

Noggin neural tube defects are not responsive to folate, and thus may be a good candidate for folate-resistant neural tube defects. A search was then made in a set of 202 humans with spina bifida, and only a single individual with a mutation was identified. However, this individual's father and unaffected sibling had the same gene change, so it may have been a polymorphism, rather than significant mutation, which was found. The conclusion is that noggin is not a major gene for causing spina bifida, but its role in anencephaly or encephalocele has not yet been investigated.

There were also two presentations by Timothy Kirkpatrick in Dr. Hope Northrup's lab and by Huiping Zhu in Dr. Richard Finnell's lab describing work on the platelet-derived growth factor (PDGF) α receptor gene. This isoform of PDGF receptor has a specific role in early embryonic development and has also been shown to have a role in neural crest cell development. The mouse mutant, Patch, lacks the PDGF-α receptor gene, and Patch and PDGFR-α knockout mice both have spina bifida.

Human YAC transgene rescued craniofacial and neural tube development in the PDGFR-α knockout mouse. So, the hypothesis was formed that if precursor cells have decreased signaling, premature differentiation may be induced; if there is increased signaling, then undifferentiation occurs, both of which could lead to neural tube defects.

A case control study looking at various alleles in PDGFR-α suggests that H1 allele looks suspicious for being a candidate in human populations, and that contrary to a study published by Joosten et al.,[1] low transcriptional activity may be associated with an increased risk of neural tube defects. In a human population, the frequency of H1 homozygotes and heterozygotes was higher in mothers of affected children and the children themselves compared to control mothers and children, although the difference was not statistically significant. Barbel Felder from Manuela Koch's lab presented her work with several candidate genes derived from animal studies, and after looking at Noggin, BMP4, Twist, and human T, found that none were good candidates, at least in terms of having a significant role in causing human neural tube defects.

Finally, Dr. Marcy Speer described her work with several candidate gene studies as well as genomic screening in human samples. She has collected a large number of samples of cases and their families, and is using several approaches in these families, which to date number 927, including 35 multiplex families with several affected family members.

Different approaches are used in analyzing these families, including association/disequilibrium studies and direct assessment of biological candidates, and identification of positional candidates via genome screening. Using this approach, several candidates, including noggin, Cyp26A1, and others have been eliminated as playing a major role in the development of human NTD.

FOLATE SUPPLEMENTATION AND FOLATE-RELATED GENES

Supplementation

As would be expected, folate supplementation studies were prominent among the presentations. Dr. Godfrey Oakley presented his plea for having as a worldwide goal the elimination of folic acid–preventable birth defects, with supplementation of food the obvious route of supplementation. The various factors that have stymied such a plan were discussed, including the arguments that only a few cases of birth defects are preventable, that there is no benefit for adults, and that there may be a hypothetical risk for adults. These can be countered by the benefits of such supplementation, including the elimination of folate deficiency and associated folate deficiency anemia in the population, decreased plasma homocysteine, and a reduction of 5% or more of deaths attributable to stroke and heart attacks. Other potential benefits would include increased genomic stability with decreased mutagenic occurrences, and decreased colon cancer and Alzheimer disease occurrences. Studies were then presented looking at effects of supplementation in various populations. Dr. David Erickson compared the effect of folic acid fortification in the United States and Chile. In the US, the FDA mandated fortification in 1998. Before fortification, the rates of NTD were $\approx$1/1000, but as high as 2.4/1000 in some areas. After fortification, rates fell by at least half. In Chile, a study looked more directly at effects of fortification. In that study, 607 females had serum folate, red blood cell folate, and vitamin B-12 measured. The levels of serum and RBC folate went up, whereas the B-12 levels remained approximately the same as before fortification. It was determined that 200 g of bread were enough to cover the recommended daily requirement for folate.

Similar results were found in the United States, in terms of increased blood folate levels. But the question, "is this enough?" can be posed. Are there subpopulations that have not benefited fully? Finally, although there has been a decrease in the frequency of spina bifida, the anencephaly rate is falling more slowly. Dr. Cynthia Moore reviewed the results of fortification in China. Before supplementation, the rate of NTD was higher in the North than in the South, sometimes by a several fold factor. After supplementation, the rate fell by 79% in the North and 41% in the South. Before supplementation, there was a female excess in the North, which disappeared after supplementation. Dr. Stevenson presented his data on the prenatal ascertainment of neural tube defects. Of those detected prenatally, 41% were liveborn (with the remaining 49% miscarried or therapeutically terminated); of the liveborns, 8% died in the first month of life. In the 263 subsequent pregnancies, the mothers took folate in 229, with no recurrent neural

tube defects. In the 34 pregnancies in which the mother did not take folate, neural tube defects occurred in 3. Dr. Laura Martinez presented the results of fortification in Mexico. Contrary to other studies, fortification did not affect RBC folate levels. However, there was also a reduction of around 50% in the frequency of NTD.

The effects of fortification on other reproductive variables was presented by Drs. Mulinare and Berry. Dr. Mulinare's work was done in part as a response to previous studies that had suggested that among women taking folate supplements, there was a 40% higher risk of having twins. He found that in all such studies, women took folate in the form of multivitamins. Therefore, he looked at the data from China, in which women were given folate only. He found that there was no difference in the frequency of multiple births between supplemented and unsupplemented groups. There is therefore no reason to believe that folate supplementation leads to an increased risk of multiple births.

Interestingly, however, in a Nepalese study, vitamin A use and beta-carotene use were associated with increased frequencies of multiple births, and both compounds are found in multiple vitamin preparations. Similarly, in response to studies suggesting that folic acid increased fertility rates and increased miscarriage rates, Dr. RJ Berry looked at these two variables in a Chinese population. Regarding fertility rates, he found that in general, folic acid helped with achieving pregnancy faster, but that effect disappeared within two years. Specifically, after 1 year, 11% had not achieved pregnancy in the folate supplemented group, whereas 19% had not achieved pregnancy in the unsupplemented group. After two years, the rates were approximately the same (2% vs. 3%).

Regarding miscarriage rates, Dr. Berry found that there was no evidence that folic acid caused an increased risk of miscarriage.

Folate-related genes

Pamela Tran, from Dr. Rima Rozen's lab, presented her work on MTHFR. MTHFR can have several forms, with a common variant, 677 C to T, associated with mild homocystinemia when folate levels are reduced. This variant has been considered a risk factor for neural tube defects. Mouse mthfr$^{+/-}$ mice can be used as a model for the 677TT human situation. In both, homocysteine is elevated to the same degree. When homocysteine levels are elevated, hypomethylation occurs; this in turn apparently has a direct effect on pregnancy. It was also presented that it is unknown how MTHFR is regulated and promoted. Future work will focus on this aspect.

Dr. Wlodarcyzk examined folate transport genes in mice, particularly the FR-α gene that has the highest binding affinity to folate. The murine homologue is folbp1. Knockout models have several abnormalities, including neural tube defects and growth retardation. In litters not supplemented with folinic acid, there were no homozygous mutants born. However, in supplemented litters, there were homozygous mutant pups born, but these often had exencephaly, encephalocele, cleft lip/palate, heart defects, etc., so folate supplementation increased survivability of abnormal embryos, although overall the frequency of NTD went down with increased supplementation.

Dr. Shaw asked the question, "how does folate exert its protective effect in humans?" He looked at the red cell folate carrier (RFC1) gene, which has a common mutation at position 80, with a G>A change. It is not known if this SNP affects transport function. So, to help address this question, he genotyped 133 children with NTD and 188 controls, with no difference found (odds ratio 1.0). The question then became whether there are other interactions at play. He found that if folate supplementation is not used, the odds ratio was 2.4 for those with the GG genotype (A is the wild type, G is the mutant), and 1.5 for those with GA. So it could be concluded that GG is not associated with an increased risk for neural tube defects per se, but could interact with reduced folate levels to increase risk. Evadnie Rampersaud in Dr. Marcy Speer's laboratory looked at human frequencies of T variants of MTHFR. In general, she found no association with MTHFR genotypes in mothers of children with spina bifida as compared to controls. Similarly, there was no apparent transmission disequilibrium of either genotype. Her conclusion was that MTHFR genotype is not a significant factor for American Caucasians.

Comments included the suggestion that if folate levels were normal, then no effect would be expected. Dr. Relton looked at both the 677 and the 1298 variants of the MTHFR gene. For 677, T is the variant, C is the wild type; for 1298, C is the variant, A is the wild type. In general, when both variants were present, red cell folate was lowest, whereas 677 variants alone were generally not associated with reduced red cell folate. Dr. Laura Mitchell presented her work on methionine synthase (MTR), which catalyzes the remethylation of homocysteine to methionine. The wild type form is A, the mutant is G. In a two step TDT, there was a slight excess of transmission of G alleles to children from mothers, but a 92% transmission rate to mothers from grandparents, which was highly significant. Methionine synthase reductase (MTRR) genotypes may also be correlated with risks of neural tube defects.

Homocysteine

The relationship between disturbed homocysteine metabolism and neural tube defect occurrence was explored by Drs. Henk Blom, Nathalie Van der Put, and Lydia Afman. Dr. Henk Blom reviewed the findings of several studies on the subject, with the conclusion that there appears to be an association between hyperhomocystinemia and the occurrence of not only neural tube defects, but also facial clefts and cardiac defects. The association between hyperhomocystinemia and recurrent pregnancy loss is less clear. The cause of hyperhomocystinemia can be attributable to mutations in several genes in the folate pathway, with good associations with MTHFR mutations and lesser associations with methionine synthase, cystathione-Beta synthase, and others in the pathway. Dr. Van der Put presented her data on 70 patients with neural tube defects, in whom homocysteine, folate, and B12 concentrations were measured. She found that there was a strong association between in-

creased homocysteine and decreased plasma folate levels with neural tube defects, whereas B12 levels were less important.

This was only partly explained by MTHFR genotypes. Lydia Afman then presented her work with chick embryos and homocysteine. She found that with increasing homocysteine levels, there was an increase in the width of the anterior neuropore and decrease in somite gain. She hypothesized that the homocysteine itself does not cause abnormalities in neural tube closure, but rather that some interference in the pathway was more likely to be related to the cause of neural tube defects.

OTHER TOPICS

Dr. John Klingensmith presented work on mouse models with holoprosencephaly, one form of neural tube defect. His particular focus was on chordin and noggin, which are both expressed in the "organizer" of the head. $Chd^{-/-}$, $Nog^{+/-}$ mice resemble human sonic hedgehog mutant heterozygotes, which is reasonable in that sonic hedgehog is downstream of chordin and noggin. Interestingly, however, $SHH^{+/-}$ mice have no phenotype, so clearly there are strain differences in gene expression. Dr. Michael Salbaum described his work on development of new techniques for looking for regulatory elements. Dr. Sally Lynch presented her work on children exposed to anticonvulsants prenatally. Among 400 pregnancies, 2 children had neural tube defects.

APPENDIX

Attendees of the 2nd International Neural Tube Defect Conference

Lydia Afman (student*), University Medical Center, Nijmegen, the Netherlands
RJ Berry, Center for Disease Control, Atlanta, GA
Henk Blom, University Medical Center, Nijmegen, the Netherlands
Abee Boyles (student), Duke University, Durham, NC
Madelyn Brouns (student), University of Maastricht, Maastricht, the Netherlands
Patricia Cogram (student), Institute of Child Health, London, UK
Andrew Copp, Institute of Child Health, London, UK
Kit Doudney (student), Imperial College, London, UK
David Erickson, Center for Disease Control, Atlanta, GA
Barbel Felder (student), Philipps-Universitat, Marburg, Germany
Marcia Feldkamp, Utah Department of Public Health, Salt Lake City, UT
Richard Finnell, Texas A&M University, Houston, TX
Barbara Franke (student), University Medical Center, Nijmegen, the Netherlands
Janee Gelineau-vanWaes, University of Nebraska, Omaha, NE
Jeff Golden, Children's Hospital of Pennsylvania, Philadelphia, PA
Nick Greene, Institute of Child Health, London, UK
Muriel Harris, University of British Columbia, Vancouver, BC, Canada
Charlotte Hobbs, University of Arkansas, Little Rock, AR
Adriane Joo (student), Texas A & M University, Houston, TX
Debbie del Junco, University of Texas, Houston, TX
Wade Junker, Texas A&M University, Houston, TX
Claudie Kappen, University of Nebraska, Omaha, NE
Tim Kirkpatrick (student), University of Texas, Houston, TX
John Klingensmith, Duke University, Durham, NC
Riko Klootwijk, University Medical Center, Nijmegen, the Netherlands
Manuela Koch, Philipps-Universitat, Marburg, Germany
Edward Lammer, Children's Hospital, Oakland, CA
Sally Lynch, Institute of Human Genetics, Newcastle upon Tyne, UK
Joyce Maddox, University of Nebraska, Omaha, NE
Laura Martinez
Laura Mitchell, Texas A&M University, Houston, TX
Cynthia Moore, Centers for Disease Control, Atlanta, GA
Joe Mulinare, Centers for Disease Control, Atlanta, GA
Robert Newell, Duke University, Durham, NC
Hope Northrup, University of Texas, Houston, TX
Godfrey Oakley, Atlanta, GA
Evadnee Rampersaud (student), Duke University, Durham, North Carolina
Caroline Relton, Westlakes Ressearch Unit, Cumbria, UK
Elizabeth Ross, University of Minnesota, Minneapolis, MN
Rima Rozen, McGill University, Montreal, CA

CONCLUSIONS

The most interesting aspect of this meeting was the interchange between individuals working with mouse models, human genes, and human responses to folate supplementation. It became clear to the participants that much could be gained from this sort of interdisciplinary discourse, in that many commented that their future research will directly benefit from these types of conferences. For example, the fact that there are several mouse models that are folate-resistant should eventually help identify why 30% of human NTD pregnancies would not be preventable. The identification of the human homolog of these mouse mutations could potentially lead to additional preventative measures such as folate supplementation is now. In addition, better understanding of how folate (or some other metabolite in the pathway) exerts its protective effect could lead to better outcomes in NTD prevention programs.

Acknowledgments

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Tom Sadler, University of North Carolina, Chapel Hill, NC
Michael Salbaum, University of Nebraska, Omaha, NE
Laurie Seaver, Greenwood Genetics Center, Greenwood, SC
Mary Seller, Guys, Kings, and St. Thomas Hospitals School of Medicine, London, UK
Gary Shaw, California Birth Defects Monitoring Program, Oakland, CA
Veronica Smith, University of Arkansas, Little Rock, AR
Marcy Speer, Duke University, Durham, NC
Andrew Spicer, Texas A&M University, Houston, TX
Ofer Spiegelstein, Texas A&M University, Houston, TX
Philip Stanier, Imperial College, London, UK
Lois Starr, University of Nebraska, Omaha, NE
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