National Children's Study Assembly Meeting
Breakout Session Summary: Exposures: Chemical and Physical
November 29, 2005
Omni Shoreham Hotel
Washington, DC

This meeting was held in conjunction with the National Children's Study, which is led by a consortium of federal agency partners: the U.S. Department of Health and Human Services (DHHS) (including the National Institute of Child Health and Human Development [NICHD] and the National Institute of Environmental Health Sciences [NIEHS], two parts of the National Institutes of Health, and the Centers for Disease Control and Prevention [CDC]), and the U.S. Environmental Protection Agency (EPA).

Co-Chair: James J. Quackenboss, M.S., Member, Interagency Coordinating Committee; Environmental Scientist, National Exposure Research Laboratory, Office of Research and Development, EPA

Co-Chair: Warren Galke, M.S.P.H., Ph.D., Environmental Epidemiologist, National Children's Study Program Office, NICHD, NIH, DHHS

Invited Participant: P. Barry Ryan, Ph.D., Rollins School of Public Health, Emory University; Member, National Children's Study Federal Advisory Committee

Invited Participant: Louise Ryan, Ph.D., Professor of Biostatistics, Harvard School of Public Health

Invited Participant: Warren Strauss, Sc.M., Program Manager, Statistics and Data Analysis Systems, Battelle Memorial Institute

Invited Participant: Ed Avol, M.S., Department of Preventive Medicine, Keck School of Medicine, University of Southern California

Context for Exposure Assessment in the Study

James J. Quackenboss, M.S., Office of Research and Development, EPA

Mr. Quackenboss explained that the breakout session on exposures would give an overview of how exposure measures were being identified for the National Children's Study (Study). Researchers have completed planning, pilots, and white papers and have attempted to identify what should be measured and how it should be studied. At this stage, researchers are seeking input from the Vanguard Centers and the research community.

Mr. Quackenboss briefly described the context for exposure assessment in the Study. The Children's Health Act of 2000 defined the parameters of the Study. It charged that the Study be a longitudinal study of environmental influences (broadly defined to include physical, chemical,

biological, and psychosocial influences) on children's health and development. The Study will evaluate the effects of both chronic and intermittent exposures on child health. Study aims—as stated in the Study Plan—are to determine the health and developmental effects related to timing, frequency, magnitude, and duration of specific exposures in children's environments.

The Study hypotheses were used to identify priority agents/chemicals and link these to outcomes. Based on a series of exposure-related "pilot studies," including white papers and articles in *Environmental Health Perspectives*, Mr. Quackenboss stressed the need for a combination of approaches in trying to get at "true exposures" that cannot be measured directly by any one method. Originally there were about 22 key Study hypotheses for environmental measurements. Since then, others have been added. The key Study hypotheses that include chemical exposure domains were identified:

- Non-persistent pesticides and poor neurobehavioral and cognitive skills
- Environmental exposures and genetic variation interactions and asthma
- Indoor and outdoor air pollution and asthma risk
- Disparities in asthma and physical environment risk factors, psychosocial stress, and health-related behaviors
- Chemical environmental agents and the endocrine system and age at puberty
- Genetics, environmental exposures, and type I diabetes
- Early exposure to bacterial and microbial products decreases risk of asthma
- Maternal subclinical hypothyroidism.

The Study's hypotheses were used to support the potential inclusion of chemicals/agents. Classes of chemicals and agents were assessed for potential measurement in environmental and biological sampling media based on whether the agent was a primary target of investigation or an important potential confounder or a key exposure the inclusion of which is needed for overall study validity. Persistence of the chemical in the body and the time pattern of exposure (that is, continuous versus intermittent) guided development of recommendations for measurement in biological and/or environmental media. The rationale for determining what and how to measure was based on a number of issues, including:

- Potential of analytical methods to identify additional analytes
- Maturity of technology
- Environmental and/or biological measurements
- Method sensitivity adequate for exposed individuals and populations
- Sampling and analytical cost
- Participant burden
- National scope of the Study
- Sample storage stability and potential for future evaluation.

Mr. Quackenboss noted that measurements are taken for prepregnancy, pregnancy, and postnatal periods. Collection points are based on the temporal and spatial variability that the agents may have as well as the ability to link from the exposure to outcomes.

Temporal Variability in Exposure and Effects Measurements in the Study

P. Barry Ryan, Emory University, National Children's Study Federal Advisory Committee Member

Dr. Ryan noted that exposure as defined in the Study Plan is divided into four main categories:

- Biological
- Chemical
- Physical environment
- Psychosocial.

Dr. Ryan's presentation began with a review of the environmental domains that were identified in the Study Plan:

- Persistent organic compounds (PCBs, organochlorine pesticides, brominated flame retardants)
- Nonpersistent, nonvolatile organic compounds (pyrethroids, phytoestrogens)
- Nonpersistent semi-volatile organic compounds (organophosphate pesticides, polycyclic aromatic hydrocarbons [PAHs], phthalates, environmental tobacco smoke)
- Nonpersistent volatile organic compounds (formaldehyde, benzene, vinyl chloride)
- Bioaccumulative inorganic chemicals (lead, mercury, cadmium)
- Nonbioaccumulative inorganic chemicals (arsenic, iron, perchlorate)
- Criteria air pollutants (ozone, particulate matter, carbon monoxide, nitrogen dioxide, sulfur dioxide).

Dr. Ryan noted that most exposure studies focus on a single contaminant, medium, and time period. This, he said, is insufficient for the National Children's Study. Study investigators are interested in more complex investigations in which multiple contaminants are studied simultaneously. Table 1 outlines the analyte class, target analytes, and related outcomes.

Table 1. Example Target Analytes

Analyte Class	Target Analytes	Related Outcomes
Allergens	Cat, dog, cockroach, dust mite, fungi, mouse/rat urine, endotoxins	Asthma
Aldehydes and ketones	Formaldehyde, acrolein	Asthma
Phenols	Bisphenol A, nonylphenol	Puberty
Bacterial and microbial products	Endotoxin (gram negative bacteria)	
Environmental tobacco smoke	Nicotine	Asthma
	Cotinine	Asthma
Metals	Pb Hg (methyl, ethyl) Hg (inorganic)	Puberty Neurodevelopmental, asthma, puberty Thyroid

	Cd in PM 2.5 As	Neurodevelopmental
PM2.5	PM mass	Asthma
Oxidants	Ozone, NO_2	Asthma
Perchlorate	Perchlorate	Thyroid
PAHs	PM	Asthma
PCBs	PCBs	Puberty, neurodevelopmental, thyroid
Dioxins/furans	Dioxins, furans	Puberty, neurodevelopmental, thyroid
Halogenated phenols	PCP, PBP	Thyroid
Phthalates	Target phthalates	Puberty
Pesticides	OPs, carbamates, pyrethroids, EBDC/ETU Atrazine DDT, DDE, other OCs	Neurodevelopmental, thyroid Puberty Thyroid
Phytoestrogens		Puberty
VOCs	Benzene Chloroform	Asthma Neurobehavioral
PBDEs	PBDEs	Thyroid, puberty
PFOA/PFOS PFBS	PFOA/PFOS PFBS	Thyroid Unknown

According to Dr. Ryan, temporal variability in exposure is of interest because it enables researchers to consider a conceptual model to relate exposures over time to health effects. The equation is as follows:

$$Effect = A\int_{-0.75Years}^{LifeDur} E(t)\, S(t)\, dt$$

In this formula:

- *E(t)* is the exposure experienced at time *(t)*
- *S(t)* is the sensitivity of the individual to exposure at *(t)*
- *A* is a constant that makes the units come out right.

This conceptual model requires *continuous* information on both exposure and sensitivity across time for an entire lifetime (including) gestation. Exposures gathered across time are thus imperative.

Dr. Ryan noted that it is possible to discretize the model as:

$$Effect \cong \sum_{AgeGroup} E(AgeGroup_i)\, S(AgeGroup_i)$$

However, researchers still require exposures to be measured at various times throughout the gestation and childhood of the participant in order to understand the impact. In the simplified model, *E(t)* is likely higher (or lower) than some threshold (or effect-level) for these time-periods:

- Exposure during pregnancy (t < 0)
- Lactation (t < 0.5)
- Early childhood (t < 3).

E(t) may have different behavior for different pollutants.

In the simplified model *S(t)* is likely to be greater during some periods of time than for others:

- First trimester (t < -0.5 yr)
- Pregnancy/gestation (t < 0)
- Lactation (t < 0.5)
- Neurological/cognitive/developmental (t < 12).

Dr. Ryan noted that several issues need to be considered in selecting an appropriate exposure assessment strategy. For one, the model must be able to integrate of environmental and biological measurements with questionnaire/diary information. Proposed measures to assess and estimate exposures should minimize error, participant burden, and costs. Another issue to consider is the role of measurement error adjustment (that is, validation studies).

Dr. Ryan noted that longitudinal studies offer good exposure estimates for epidemiology. They can provide detail on:

- Secular trends in exposure
- Seasonal patterns (weather, source variability, activities)
- Long-term (and short-term) effects of control strategies
- Effects of new sources and patterns.

Weaknesses of longitudinal studies include:

- Possible reduction in power due to reduction in sample size
- Difficulty in maintaining a cohort
- Effects on analysis complexity due to dropouts, and so on (epidemiologists know how to adjust for this).

The power of the study design for longitudinal studies of exposure is dependent upon the ability of researchers to perform a number of tasks. This includes the proper selection of participants, the ability to maintain the cohort over time, and the ability to account for changes in sample size. However, the increasing level of detail is often associated with increased costs/burden. Options for selection of measurements include:

- Method (sampling, analytical) specifications for accuracy, precision, detection limits, and so on
- Frequency of measurement (relative to temporal variability) and number of sampling locations (that is, within the home)
- Selection of media (for example, by life stage) and chemicals and agents relative to true exposure (and dose) and to priority outcomes
- Scale of measurements (such as regional, community, household, individual).

Dr. Ryan concluded that it is possible that a model such as $Effect = A\int_{-0.75Years}^{LifeDur} E(t)\, S(t)\, dt$ is reasonable, thereby necessitating the repeated measure, longitudinal approach. Toward this end, study investigators will visit households and examine children repeatedly over a 21-year period. This will supply invaluable information on trends in exposure, temporal variability in exposure, and the association between such variability and health outcomes. Such data will be invaluable in assessing health outcomes associated with environmental exposure in this vulnerable population.

Development of Cost Effective Statistical Sampling Strategies and Optimal Design Considerations for Exposure Assessment as Part of the National Children's Study

Louise Ryan, Ph.D., Professor of Biostatistics, Harvard School of Public Health, and Warren Strauss, Sc.M., Program Manager, Statistics and Data Analysis Systems, Battelle Memorial Institute

Dr. Ryan explained that exposure assessment design requires researchers to identify sources of bias in relationships, including nonresponse and measurement error. The design must also provide adequate statistical power while minimizing the burden on participants. There are several strategies for selecting participants for rigorous exposure assessment, as there are for developing cost-effective statistical sampling strategies and optimal design.

To illustrate one possible strategy, Dr. Ryan provided a hypothetical example. Researchers are interested in the effects of *in-utero* pesticide exposures on autism. Of the 64,930 subjects without household pesticide use, there are 70 reports of autism. Of the 34,770 subjects reporting household pesticide use, 230 report autism. If there are resources to measure aggregate exposure on 300 subjects, who do researchers pick? How can they use questionnaire data to guide their selection and improve the analysis?

A multistage sampling paradigm offers the answers. In stage I sampling for the study, y (autism) and z (pesticide usage) are measured for the population of interest (all children). In stage II sampling, x (aggregate exposure) is measured. In subsequent validation substudies, researchers select a sample to provide information related to the bias or error introduced into the main study cohort by the nature of the design. The information is gathered from the validation sample designed to allow for appropriate statistical adjustments to the data collected in the larger cohort to address bias and error.

Dr. Ryan suggested that the example above could be applied to other scenarios where:

- *X* is the "gold-standard" measure of exposure
- *Y* is the health outcome of interest
- *Z* is the less precise measure of exposure.

X is measured on a small subset of the cohort, whereas *Y* and *Z* are measured on the entire cohort. Three general methods for selecting the subset of study participants that are in the validation sample (that is, have both *Z* and *X*):

- Outcome dependent
- Covariate dependent
- Random sampling.

According to Dr. Ryan, the project has developed optimal design strategies by using a maximum likelihood approach and finding the sampling design that minimizes the variance of the estimated quantity of interest.

This design offers:

- Cost savings
- Potential to minimize burden to participants
- The possible use of a smaller preconception validation sample
  - Use of retrospective measures of exposure for the main cohort
  - Corrections for temporal variability
- Careful planning in the study design to ensure that appropriate relationships between measurements are captured.

Mr. Strauss presented an overview of new work developing software for assisting in decision-making regarding exposure assessment design. Battelle and Harvard are jointly developing a prototype software tool to allow Study planners to research benefits and limitations of utilizing study designs that employ validation sampling techniques. The tool contains an interface that sequentially interviews the user on critical design input regarding the health outcome, exposure, type of relationship between exposure and outcome, potential measurement methods for exposure, sample size, and resource constraints. Output is provided on cost, sample size, and power across a range of designs.

Mr. Strauss presented a typical decision pathway for the Study's environmental exposure assessment:

- **Step 1:** Characterize True Exposure (x) (single versus repeated exposures, cross sectional exposures, longitudinal exposures)
- **Step 2:** Characterize Effect Modifier ($e|x$)
  - Effect modifier (e) may be factors such as genetic predisposition to disease
  - Define whether effect modifier is continuous or categorical
  - Define the relationship between effect modifier and true exposure x ($e|x$)

- In many cases, may expect exposure and the effect modifier to be independent (example of relationship: e = allergic sensitivity to cat dander [effect modifier], and x=exposure to cat allergens. There is likely a negative association between e and x.).

- **Step 3:** Characterize Outcome Measures ($y|x$; $y|x,e$) (frequency of individual outcomes measures [single, cross sectional or repeated, longitudinal]).
- **Step 4:** Characterize Measurement Methods (z/x) (for each measure of exposure the user will provide inputs on relationship with x, costs, detection limits, possibility of archiving samples for future analysis, possibility of collecting following another exposure measure).

Following these steps, the Battelle Validation Sampling Assessment Tool is used for optimal design recommendations for the Study exposure assessment. Mr. Strauss outlined several examples of how the tool could be applied.

Mr. Strauss concluded by stating that validation sampling may allow the Study to conduct more cost-effective data collection while still retaining necessary power to make conclusions about study hypotheses. Battelle's automated tool for considering various sampling design options will allow planners and protocol developers to identify optimal sampling strategies using validation studies. Designs are highly sensitive to design input. Pilot studies to identify appropriate surrogates (and relationship with true exposure) will be key.

Hierarchical Approaches to Exposure Assessment: Lessons Learned from the Children's Environmental Health Centers

Ed Avol, M.S., Department of Preventive Medicine, Keck School of Medicine, University of Southern California

Mr. Avol opened his presentation with a brief discussion of measurements, modeling, and modifiers. He stressed that exposure has to be measured at different levels, including where the child lives, attends school, and plays. Regional differences are also factors. For example, sulfates predominate in the northeast and nitrates in the northwest. Identifying broad areas of pollutants and exposures helps researchers to identify populations to study. To illustrate, he pointed to the lessons learned from the Children's Health Study, with which he has been involved for several years.

The aim of the Children's Health Study is to assess multiple sources of exposure. This includes:

- Ambient levels (continuous and 2-week)
- Lifetime residence history
- Time-activity and household characteristics (where children spend their time)
- Sample measurements (micro-environmental and regional)
- Geographic Information System based assessments of traffic density and pollutant dispersion modeling
- Local variability in ambient pollution levels.

Based on these complex variables, researchers were able to plot exposures to show local variability in ambient pollution levels. Mr. Avol demonstrated this variation through a graph of

community exposure over time. This range of variability is important in teasing out differences in health outcomes. The Children's Health Study examines three levels of comparisons:

- Between communities (ambient)
- Between children within communities (personal, spatial, traffic density, and so on)
- Between times within children or communities measured annually (such as lung function, symptoms) and daily (such as school absences).

The analysis was conducted using multilevel random effects models incorporating all three levels of comparison. Based on Children's Health Study data, Mr. Avol demonstrated the importance of proximity to freeways in terms of exposure to ultrafine particles. Researchers also measured gases over several weeks in children's homes as well as in the community. Again, there was considerable intercommunity variability. For asthma, there was an association between NO_2 and distance to roadways. The question, however, is whether NO_2 has a health impact. Mr. Avol suggested that it is more likely that NO_2 is highly correlated with other pollutants that are from similar sources that behave similarly. Therefore, it is likely that the adverse health effects are related more to traffic than to the effect of NO_2, illustrating the importance of not overinterpreting.

Mr. Avol presented data on the correlations among Children's Health Study community pollutants and spatial variability of measured pollution and traffic density. He suggested that there are a number of substudies that are feasible. He cautioned, however, that there are many modifiers and confounders that need to be addressed. To demonstrate, he noted several other risk factors for asthma, including humidifiers, pets, obesity, maternal exposure, and activity.

Discussion

Session presenters responded to questions and comments from participants concerning the following issues:

- *What would be lost by using the more cost-effective methodology.* Mr. Strauss explained that there is a potential large cost savings for an outcome-dependent sample. Researchers cannot test every possible outcome for every possible exposure. The research is hypothesis driven. Mr. Quackenboss added that the Study cannot support the gold standard for every measure. This is a reasonable, cost-effective alternative that allows us to make decisions based on their impact on meeting Study objectives.

- *Why the sample for pollution exposure data was 220.* Mr. Strauss agreed that researchers will have to look at the numbers and reevaluate.

- *The assumption that outcomes will be consistent across contaminants.* Mr. Strauss noted that the tool was made to help researchers look at one outcome at a time.

- *The methodology assumes that exposure is the most important variable.* Mr. Strauss explained that researchers know the prevalence of genetic polymorphisms of interest and can design the methodology accordingly.

- *Why some obvious variables were missing, such as radiation, which evidence suggests can have cumulative effects.* Mr. Quackenboss noted that the hypotheses came through Working Groups and collective experience at the time the Study was designed. Variables may be added as the Study evolves, but any additions need to be considered very carefully.

- *The presenters raised many problems, including polymorphisms, timing of exposures, metabolites in urine, and so on; however, no solutions were given.* Mr. Quackenboss explained that researchers recognize that all of the measurements have associated error. A variety of tools will be used to gain the best possible data, given financial constraints.

- *The cost effective approach may not be the best one and the more costly approach would give more answers at once.* Mr. Quackenboss said that researchers found that they could not identify methods if they did not start to narrow the list. He added that the hypotheses were developed years ago, based on the science at the time. Researchers started the series of hypotheses and identified what could be collected, how it should be stored, and so on. There may be unexpected results that require additional hypotheses. There may be new techniques that allow different kinds of studies. For such instances, researchers will have stored samples from subjects; however, it is not possible to store some types of environmental samples for long time periods, depending on the stability of chemicals in those samples.

- *Whether the methodology presented in Mr. Strauss' presentation compromised on important points.* Mr. Quackenboss explained that Mr. Strauss' presentation was merely using examples to demonstrate that it is possible to look at a continuum of measures with precision. Researchers can pay more to get incremental results, but it is unclear that this is the best use of limited funds. He noted that the true gold standard is what Dr. Barry Ryan described as taking continuous measurements of a lifetime. Researchers want to be able to consider the impact of decisions on measurement errors. Validation is one part of that, but it is not the only application of the measurement error approach. He agreed that researchers need to be careful. Mr. Strauss added that the research requires a careful balancing act between including key objectives and achieving the goal of being a resource for future studies. He said that the tool developed will enable researchers to identify the minimum statistically required sample sizes for alternative measurement methods and designs.

Additional Participants

Session A:

Ruth H. Allen, Ph.D., M.P.H., Office of Pesticide Programs, EPA
Michael Aschner, Ph.D., Kennedy Center for Research on Human Development, Vanderbilt University Medical Center

Tina Bahadori, Sc.D., Long-Range Research Initiatives, American Chemistry Council
Dean Baker, M.D., M.P.H., Center for Occupational and Environmental Health, University of California, Irvine
Cynthia F. Bearer, M.D., Ph.D., Rainbow Babies and Children's Hospital, Case Western Reserve University
Stephen J. Bedosky, P.G., M.S., LFR Levine Fricke
Nicolette T. Borek, Ph.D., National Institute on Drug Abuse, NIH, DHHS
Ruth A. Brenner, M.D., M.P.H., NICHD, NIH, DHHS
R. Lorraine Brown, R.N., B.S., Maternal and Child Health Bureau, HRSA, DHHS
Sarah H. Brozena, J.D., American Chemistry Council
Thomas M. Burbacher, Ph.D., Department of Environmental and Occupational Health Services, University of Washington
Richard Callan, M.P.H., Office of Research and Development, EPA
Jen Jen Chang, Ph.D., Department of Community Health in Epidemiology, Saint Louis University
Debra Cherry, M.D., M.S., Department of Occupational Health Sciences, University of Texas Health Center, Tyler
Gwen W. Collman, Ph.D., NIEHS, NIH, DHHS
Mary Ann Danello, Ph.D., Health Sciences, U.S. Consumer Product Safety Commission
Andrea DeSanti, Business Development, Fisher BioServices
Sharon M. D'Orsie, D.Sc., Department of Environmental Science, University of Southern Maine
Jonas H. Ellenberg, Ph.D., Department of Biostatistics, University of Pennsylvania School of Medicine
Nigel A. Fields, Office of Research and Development, EPA
Judith A. Graham, Ph.D., Long-Range Research Initiative, American Chemistry Council
Rajsree Gupta, Ph.D., M.B.A., Platypus Technologies
Jeanne Hewitt, Ph.D., Milwaukee Institute of Environmental Health, University of Wisconsin, Milwaukee
David E. Hrdy, B.S., Office of Prevention, Pesticides, and Toxic Substances, EPA
Edward W. Kantor, B.S., National Exposure Research Laboratory, EPA
Karen L. Lakin, M.D., M.S.P.H., LeBonheur Children's Medical Center, University of Tennessee Health Science Center
Rod Larson, Ph.D., M.S., C.I.H., Department of Family and Preventive Medicine, University of Utah Health Sciences Center
Mark Maier, Ph.D., CropLife America
Marcia F. Marks, A.C.S.W., Environmental-Health/Policy, PA County Commission on Health
Daniel Michael, M.S., Neptune and Company, Inc.
Andrew Newcombe, Agricultural Studies Group, Levine Fricke
Charles Nozicka, D.O., Pediatric Center of Exellence, Alexian Brothers Health System
Barbara O'Brien, M.P.H., National Children's Study Coordinating Center, Westat
Andrea J. Pfahles-Hutchens, M.S., Office of Prevention, Pesticides, and Toxic Substances, EPA
Marc L. Rigas, Ph.D., Center for Scientific Review, NIH, DHHS
Christine K. Robles, OTR/L, M.P.H., Office of Research and Development, EPA
Marian K. Stanley, B.S., M.B.A., CHEMSTAR, American Chemistry Council

Susan Marie Viet, Ph.D., C.I.H., National Children's Study Coordinating Center, Westat
Eleanor A. Vine, M.S., Montgomery County, PA Health Department
Ann M. Vinup, Research Committee, Learning Disabilities Association of America
Bryan Williams, Ph.D., Department of Epidemiology and Biostatistics, University of Tennessee Health Science Center
Alan D. Woolf, M.D., M.P.H., Department of General Pediatrics, Children's Hospital and Harvard University

Session B:

Sheryl Bartlett, Ph.D., Healthy Environments and Consumer Safety Branch, Health Canada
Christine Cronk, Sc.D., Department of Pediatrics, Medical College of Wisconsin
Victoria Dergileva, B.Sc., Information Technology, Booz Allen Hamilton, Inc.
Alan R. Fleischman, M.D., NICHD, NIH, DHHS
Alexa Fraser, Ph.D., Environmental Studies, Westat
Christine Cole Johnson, Ph.D., M.P.H., Josephine Ford Cancer Center, Henry Ford Health System
Steven Leuthner, M.D., M.A., Department of Pediatrics, Medical College of Wisconsin
Melina S. Magsumbol, M.A., Department of Preventive Medicine, University of Tennessee Health Science Center
Akihiko Noguchi, M.D., M.P.H., Department of Pediatrics, Saint Louis University
Rosemarie G. Ramos, Ph.D., M.P.H., NIEHS, NIH, DHHS
Offie P. Soldin, Ph.D., M.B.A., Department of Medicine, Georgetown University Medical Center
Douglas W. Stewart, D.O., M.P.H., Department of Pediatrics, University of Oklahoma Health Sciences Center
Katherine A. Surman, B.S.N., M.S.A., Office of the Assistant Secretary of Defense, U.S. Department of Defense
Carol Sweeney, Ph.D., Family and Preventive Medicine, University of Utah School of Medicine