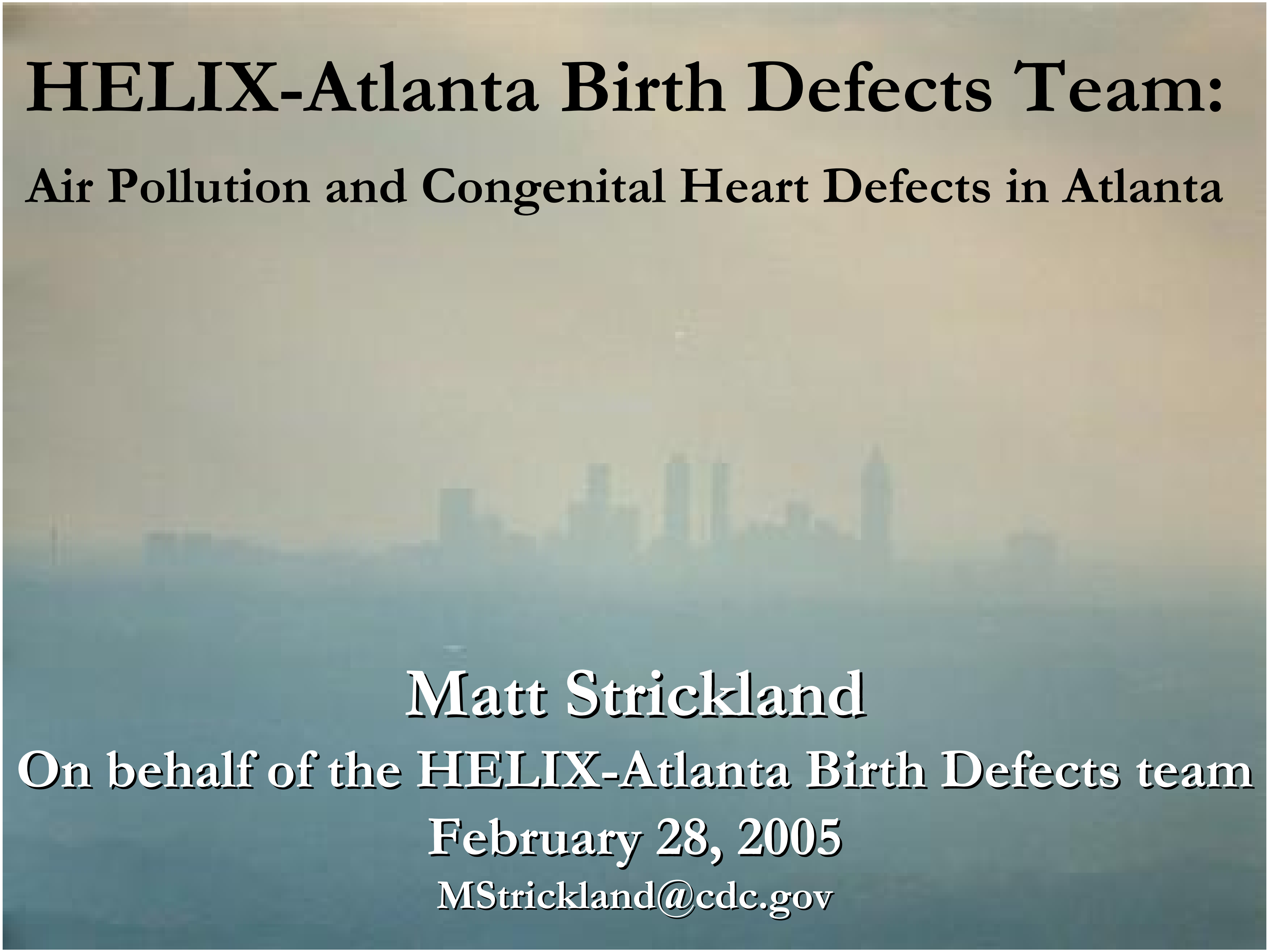

HELIX-Atlanta Birth Defects Team:

Air Pollution and Congenital Heart Defects in Atlanta

Matt Strickland

On behalf of the HELIX-Atlanta Birth Defects team

February 28, 2005

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Purpose

- HELIX (Health and Environment Linked for Information eXchange)-Atlanta:
  - Microsystem of National EPHT effort
  - Similar to other state grantee demonstrations
  - 1 of 6 projects
  - http://www.cdc.gov/nceh/tracking/helix_overview.pdf
- Birth Defects Team:
  - Integrate ambient air pollution data with the underlying cohort of births, fetal deaths, and congenital heart defects in 5-County Atlanta during 1994-2002

Epidemiologic Studies

- Smoking
  - Inconsistent associations
  - VSD, pulmonary stenosis, conotruncal defects
- Ambient air pollution
  - Two ecological studies
  - One case-control study
    - Objective: Evaluate the effect of air pollution on the occurrence of heart defects & orofacial clefts

Case-control study – Ritz et al. (2002)

CASES

- California Birth Defects Monitoring Program
  - 1987-1993
  - 4 counties
- Fetal deaths & live births
  - 1+ heart defect
  - 20 weeks gestation – age 1
  - Linked with vital records, complete data
  - Within 10 miles of a monitoring station
- 6 heart defect groups

Case-control study

SAMPLED CONTROLS

- Fetal deaths & live births
  - Same time period & zip codes
  - Linked with vital records, complete data
  - No birth defects
  - Sample of ~10,000

Case-control study

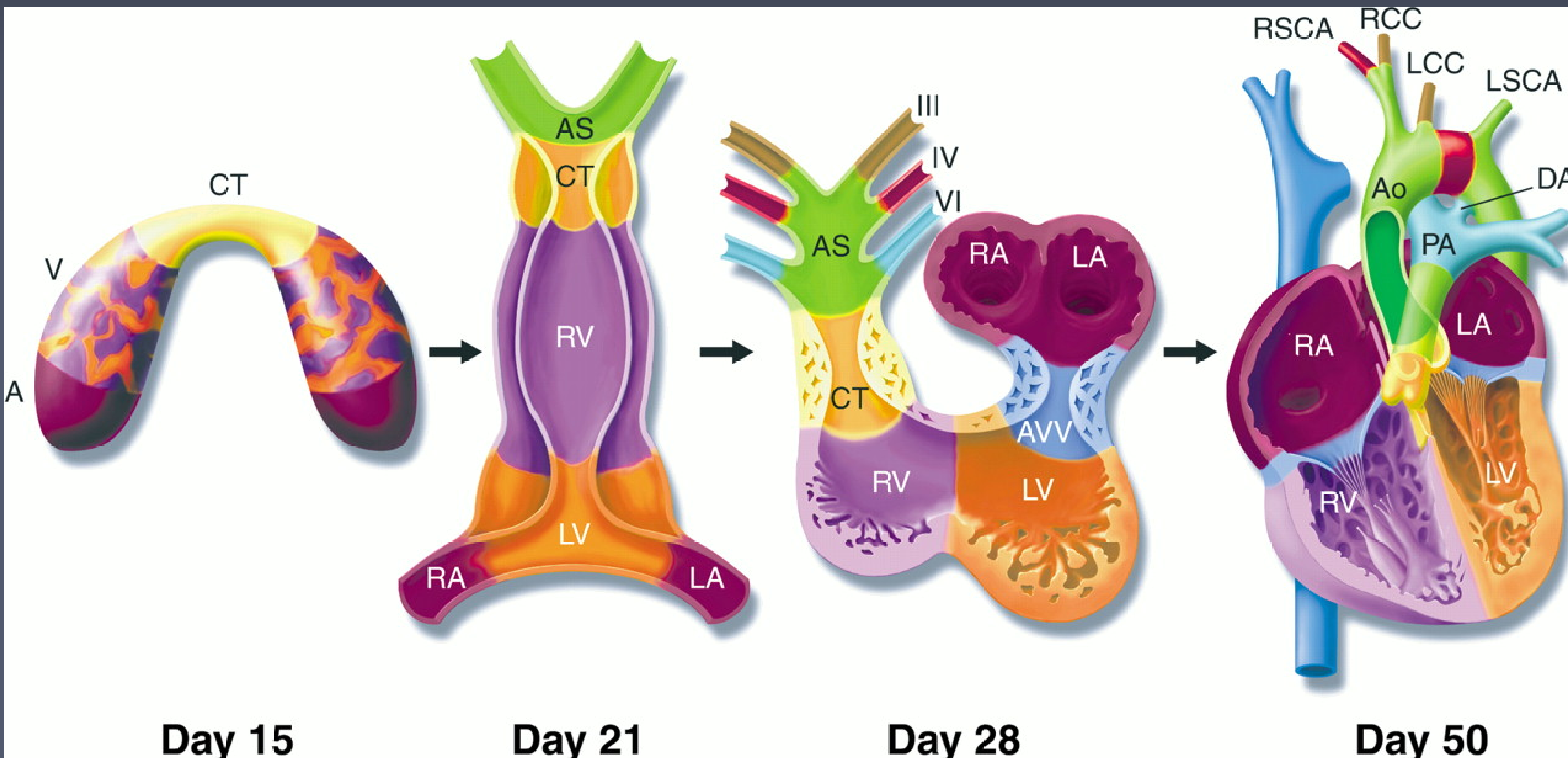
POLLUTION

- CO, NO_2, O_3, and PM_{10}
- Most relevant monitoring station
- Ambient pollution averaged:
  - 1st, 2nd, & 3rd month of development
  - 2nd & 3rd trimesters
  - 3-month period prior to conception

Results – Ritz et al. (2002)

	Ventricular septal defects (n=260)	Aortic artery and valve defects (n=276)	Conotruncal defects (n=152)	Pulmon. artery & valve defects (n=209)
CO				
2nd month				
Quartile 1	1.00	1.00	1.00	1.00
Quartile 2	1.62 (1.05, 2.48)	1.10 (0.73, 1.66)	0.90 (0.55, 1.47)	1.09 (0.69, 1.73)
Quartile 3	2.09 (1.19, 3.67)	1.25 (0.74, 2.13)	0.75 (0.39, 1.45)	0.92 (0.50, 1.70)
Quartile 4	2.95 (1.44, 6.05)	0.93 (0.47, 1.85)	0.79 (0.35, 1.78)	1.00 (0.46, 2.17)
Ozone				
2nd month				
Quartile 1	1.00	1.00	1.00	1.00
Quartile 2	1.21 (0.73, 2.01)	1.19 (0.71, 2.01)	1.63 (0.83, 3.23)	1.36 (0.76, 2.43)
Quartile 3	0.94 (0.46, 1.91)	1.69 (0.84, 3.42)	1.98 (0.74, 5.31)	1.42 (0.62, 3.23)
Quartile 4	1.13 (0.50, 2.54)	2.68 (1.19, 6.05)	2.50 (0.82, 7.66)	1.99 (0.77, 5.13)

Heart Development



Srivastava (2001) *Ann. Rev. Physiol, 451*

Possible Mechanism for Air Pollution & Birth Defects?

- Ozone
  - Neural crest cells
    - Vulnerable to toxic insults → apoptosis
    - Lack antioxidative stress proteins
    - Ozone is a strong oxidizing agent
  - Inflammation
- Carbon Monoxide
  - Decreases placenta metabolic & transport functions
- Surrogate for other pollutants
- Multiple comparisons

Spatial Confounding?

- Risk factor has spatial variation
  - Uncontrolled maternal diabetes
- Pollution has spatial variation
  - Multiple monitors
- Correlation
- Remedies?
  - Control for risk factors
  - Central monitor

Demonstration Project Overview

- Compile retrospective cohort, 1994-2002
  - Births
  - Fetal deaths
  - Heart defects
- Obtain ambient pollution measurements
  - Average over days 16-43 of development
- Group similar cases for analysis

Birth Defects

Metropolitan Atlanta Congenital Defects Program (MACDP), NCBDDD, CDC

- Active surveillance
- Clayton, Cobb, DeKalb, Fulton, Gwinnett
- Presence of serious or major structural defect
- 20 weeks gestation – age six

Selected Cases for Surveillance

- Date of birth/fetal death 1994-2002
- 1+ heart defect
- Exclusions:
  - Chromosomal anomalies
  - Syndromes
- Complete data
  - Date of birth/fetal death
  - Gestational age

Vital Records

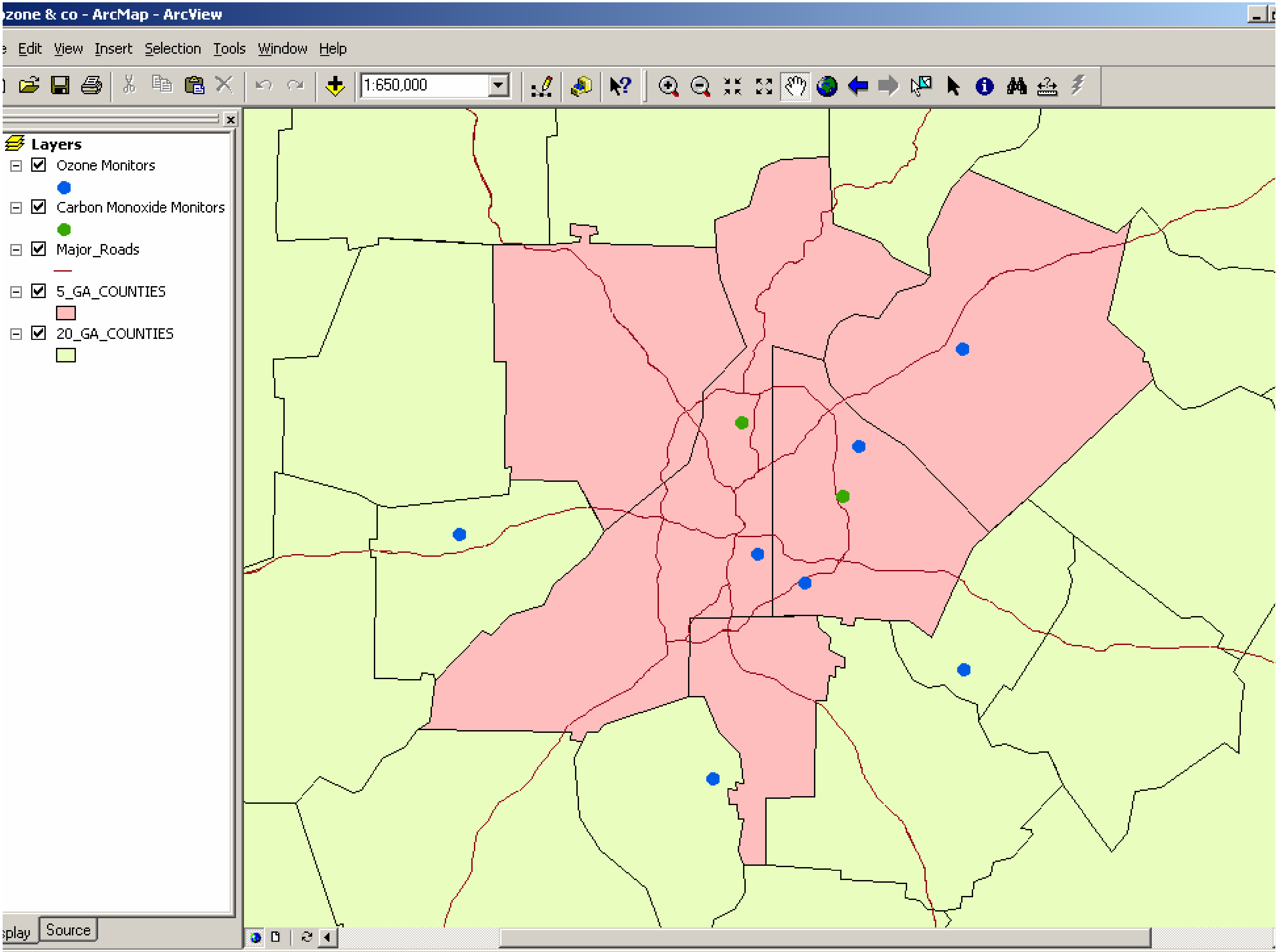
- Office of Health Information and Policy, GA Division of Public Health
- Linked with MACDP data at CDC

Time-series	
Date of birth/fetal death	Gestational age

Spatio-temporal	
Geocodes	Liveborn/stillborn
Maternal age	Previous preterm delivery
Maternal ethnicity	Pregnancy complications
Infant gender	Pregnancy risk factors

Estimating Exposure Window

- Subtract gestational age (in days) from birth date to get estimate of last menstrual period date (LMP).
- Assumption: Conception occurs 14 days after LMP.



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Characterize Ambient Pollution Levels

- Primary approach: time-series
  - Representative, centrally located monitor
  - Daily measurements
  - Average during days 16-43
- Other approaches:
  - Average across monitors
  - Use closest monitor
  - Surfacing algorithm
    - Ozone
    - NASA

Coding & Classification of Birth Defects

- Up to 24 defect codes per infant
- 6-digit BPA code
- 48% of affected infants have 2+ cardiac defect codes
  - How do you classify infants with 2+ codes?

Issues in Classification

"How to group a [cardiac] defect has been a major challenge to investigators. Schema that aid the pathologist and surgeon serve the epidemiologist poorly…classification of heart defects by anatomic features may obscure developmental relationships"

- Ed Clark (1996) *Sem. in Perinatology 20: 465-72*

"A continuing challenge among birth defects epidemiologists is the classification of congenital heart defects into etiologically meaningful groups"

-Martha Werler (2001) *Epidemiology 12: 482-84*

Heart Defect Classification

Creating outcome groups for epidemiologic analysis is a two-step process

1. Classify infant
2. Group embryologically similar infants

Step 1: Classify the infant

- Congenital Heart Surgery Nomenclature & Database Project
  - International effort
  - Standardize nomenclature & reporting
  - Under development
  - As of 2/22/2005: 1536/3819 cases (40%)

Mavroudis, C. & Jacobs, J.P. (2000). Congenital Heart Surgery and Nomenclature Database Project: overview and minimum dataset. Ann. Thoracic Surg., 69, S2-S17.

Microsoft Access - [Assignments]

File Edit View Insert Format Records Tools Window Help

CDCID 034399 ? Assigned To 1 Lorenzo Botto Birth Year 1994 Gest Age 35 Birth Wt 2126 Sex 1 Male Outcome 1 Live Born

Heart Defects

DefCode	Verb	Description
747230	☐	Persistent Right Aortic Arch
747250	☐	Vascular Ring
	☐	

Group

- Anomalous Syst Venous Conn
- Aortic Valve Disease
- AP Window
- ASD
- AV Canal
- Cardiomyopathy
- Coarc of the Aorta (all types)
- Congenitally Correctced TGA
- Cor Triatriatum
- Coronay Artery Anomalies
- DOLV
- DORV
- Electrophysiologic
- Heterotaxia
- Hypoplastic Left Heart Syndrome
- Interrupted Aortic Arch
- LV to Aorta Tunnel
- Miscellaneous, Other
- Mitral Valve Disease

Class Code

0010	PFO (gest age: >=36 wks; >=6 wks)
0020	ASD, secundum
0030	ASD, sinus venosus
0040	ASD, coronary sinus
0050	ASD, common atrium (single atrium)
0060	ASD, NOS
0070	VSD, Typ I (subart,supracr,c sep,infund)
0075	VSD, Typ II (perimembranous)
0080	VSD, Typ III (inlet)
0085	VSD, Typ IV (muscular)
0086	VSD, restrictive / small
0090	VSD, NOS
0100	AVC (AVSD), complete CAVSD
0110	AVC (AVSD), intermed (transitional)
0120	AVC (AVSD), partial (ASD, primum)
0130	AVC (AVSD), NOS
0140	AP window (aortopulmonary window)
0150	PA origin from asc aorta (hemitruncus)
0160	Truncus arteriosus

Heart Complexity

- Simple
- Association
- Complex

Non-heart Complexity

- No Other Defects
- Multiple Defects
- Syndrome
- Association
- Unclassified

Non-Heart Defects

DefCode	Verb	Description
194000	☐	Neuroblastoma
747500	☐	Single Umbilical Artery
749290	☐	Cleft Lip, NOS, w/Cleft Palate
750310	☐	Esophag Atresia w/Ment of T-E fistula
751100	☐	Stenosis/Atresia/Absence of Duodenum

Classification

Code	Description

Remove

Clinical Diagnosis Only ☐

Reviewed ☐

Comment

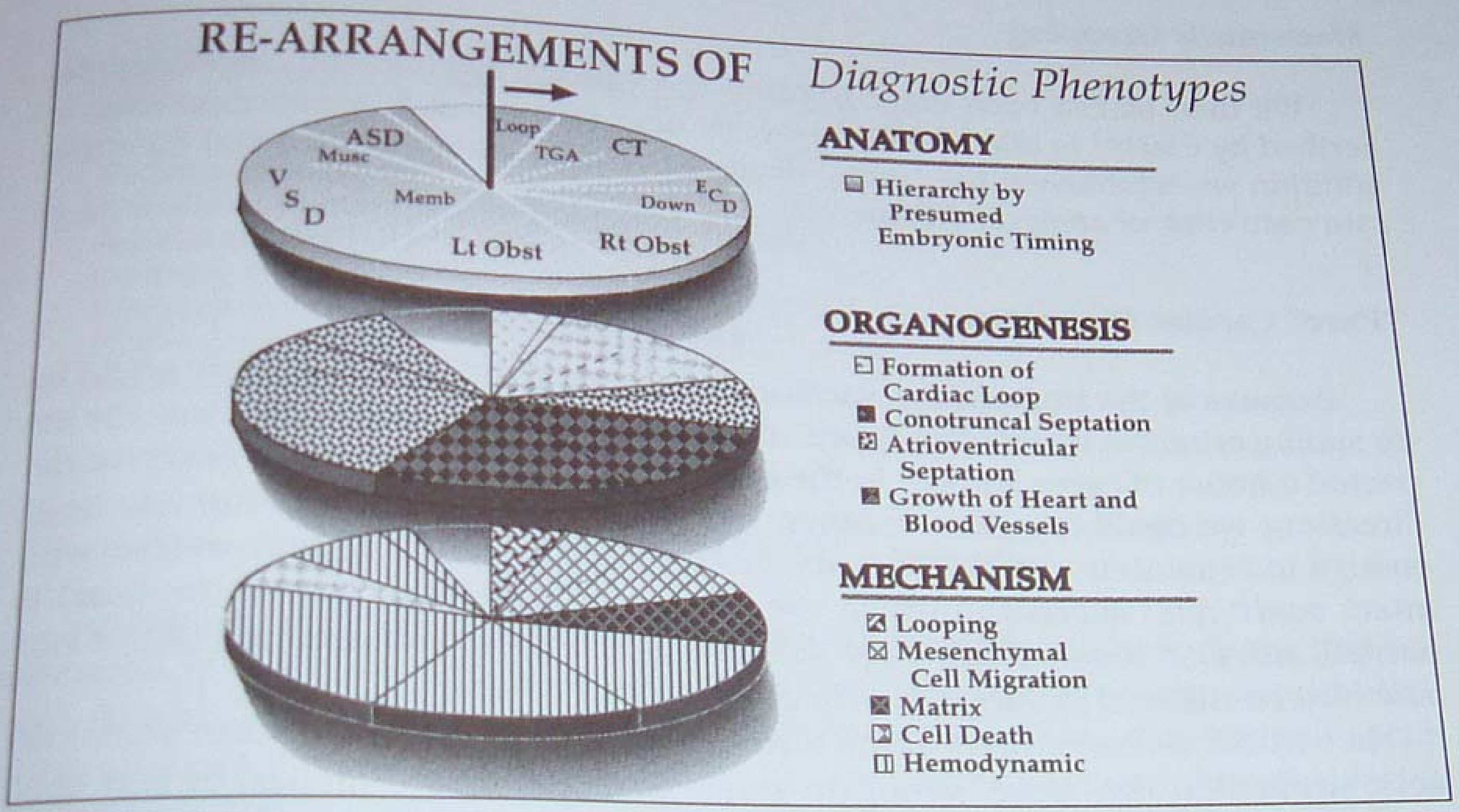
Detailed Description

Example Case

- Unbalanced complete AV septal defect
- Hypoplastic left atrium and ventricle
- Double outlet right ventricle
- Mitral valve atresia
- Hypoplastic transverse aortic arch
- Coarctation of the aorta

Step 2: Group infants for analysis

Ferencz et al. (1997) *Epidemiology of Congenital Heart Disease: The Baltimore-Washington Infant Study, 1981-1989*



Data Integration

- Integration based on:
  - Dates (for temporal data)
  - Date & geocode (for spatio-temporal data)

Geocoding Validation

- Assess the validity of MACDP geocodes using GIS methods
- Data sources:
  - USGS orthophoto data
  - Tax parcel data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Evaluate Utility of Linkage and Sustainability

- Review process and results of project
- Evaluate process for surveillance purposes
- Identify PHIN compatibility issues
- Document

Disseminate Results

- Presentations
  - Webinars
  - EPHT Conference in April
  - TBD…
- Outreach team
  - Katie Kilker (CDC)

Team Members

CDC

- Matt Strickland
- Adolfo Correa
- Csaba Siffel
- Randolph Daley
- Alissa Berzen
- Amanda Sue Niskar
- Katie Kilker
- Gabriel Rainisch
- Lorenzo Botto

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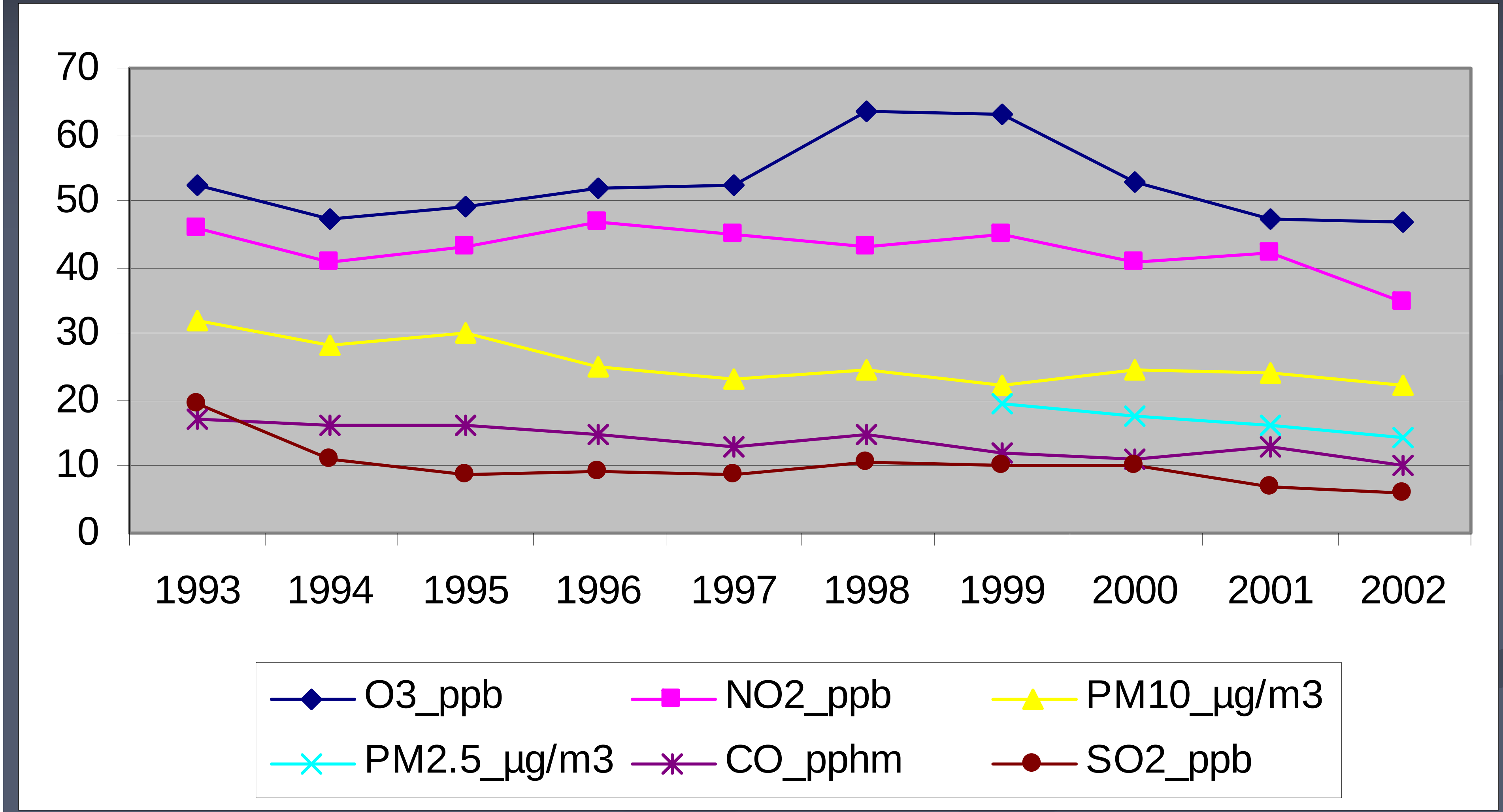
- Solomon Pollard (EPA)
- Paige Tolbert (Emory)
- Bill Mahle (Emory)
- Mark Reller (Oregon Health & Science University)

Extra Slides

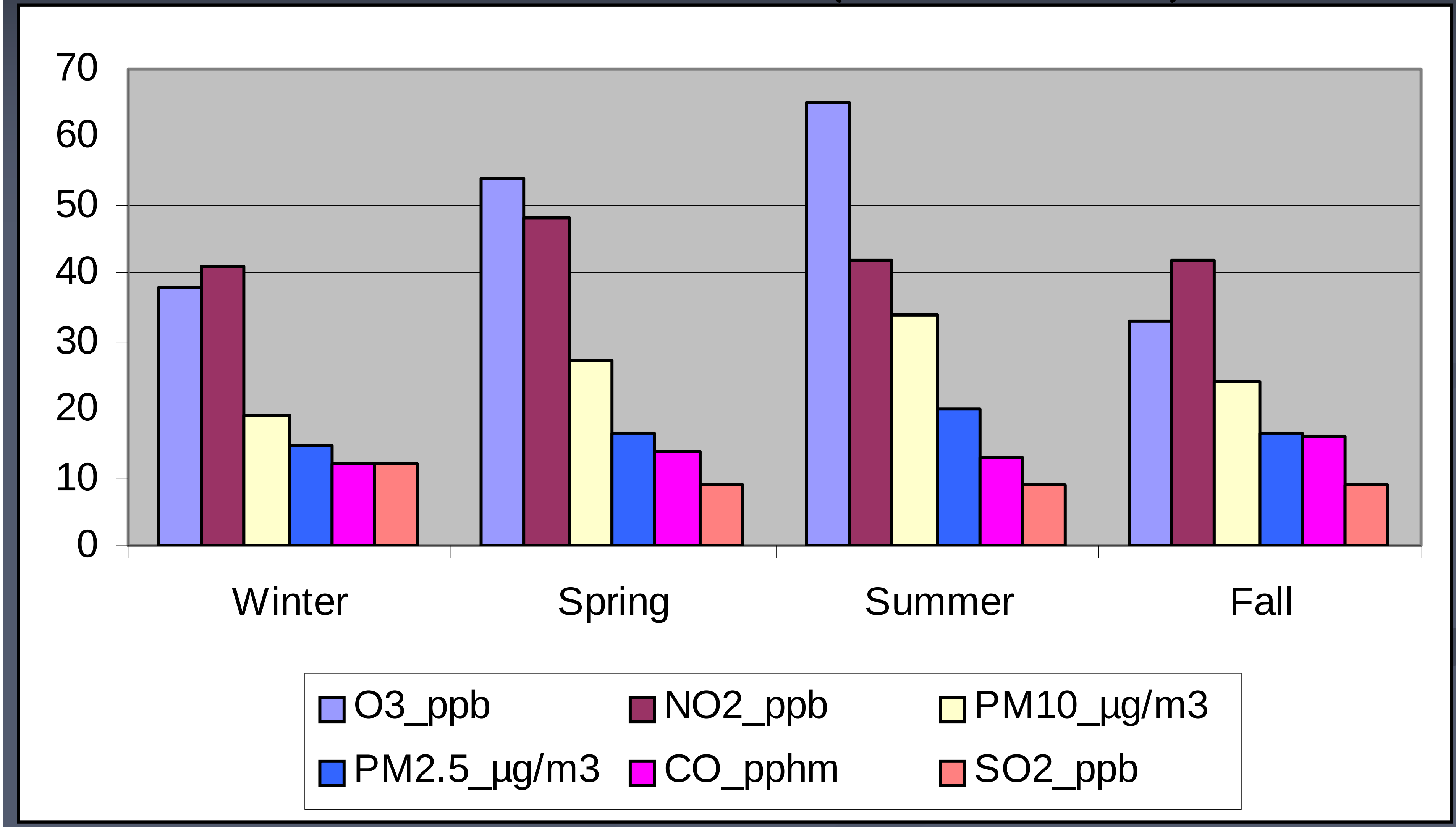
Animal Studies

- Smoking
  - Not a strong teratogen
  - DNA damage, cell migration & survival
- Carbon monoxide
  - Skeletal malformations
  - Toxic to nervous system
  - Protein deficiency → increased risk of birth defects
- Ozone
  - High levels kill rat embryos
  - 400 ppb → 85% reduction in serum retinol concentration

Median Annual Air Pollution Levels, Atlanta



Median Seasonal Air Pollution Levels, Atlanta (1994-2002)



1) In the setting of double outlet right ventricle (DORV) or single ventricle, we will only use the code for sub-valvar PS (490) even if there is multi-level obstruction including valvar PS.

2) We will use the code for bicuspid aortic valve (555) when only mild AS is present as defined by an echo Doppler gradient of <2.5 m/sec (or cath <20 torr). If a more significant degree of stenosis is present, than the valvar AS code (560) should also be used.

3) For the VSD codes, we would like to be able to distinguish "small, restrictive" (86) in addition to the anatomic sub-type. This code will most typically be used in conjunction with the code for muscular (85) or perimembranous (75).

4) When a patent foramen ovale (PFO) is nearly always present with another lesion, such as tricuspid atresia, it will not be marked as a separate diagnosis. In reality, this code will be used infrequently.

5) When a patent ductus arteriosus (PDA) is present in the setting of critical neonatal lesions such as HLHS, coarctation, or pulmonary atresia, it will not be coded.

6) When the diagnosis of discrete coarctation is made (990), we will not use the code for aortic arch hypoplasia (1000) as this finding is invariably present in varying degrees in this setting. This latter code will be used when it is the only descriptor present in the ROCR.

7) The code discrete subvalvular aortic stenosis (565) should only be when a discrete membrane or ridge is present. For example, it should not be used in the setting of hypertrophic cardiomyopathy with sub-aortic obstruction.

8) When the code for HLHS is used (730), we will not use any of the additional codes for AS, mitral atresia, or coarctation.

9) In the setting of the DORV variant of mitral stenosis/atresia and hypoplastic LV with normal aorta, use the appropriate DORV code and the code for Single Ventricle and mitral atresia (810). If the aorta is atretic (and a Norwood would be the appropriate operation), use the HLHS code (730) with the DORV code.

10) Tracheal compression that is due to abnormal origin of the innominate (brachiocephalic) artery should not be coded as a vascular ring.

11) Pulmonary artery stenosis (PPS) should not be coded in infants less than 6 weeks of age (analogous to the rules used for PDA and PFO).

12) If no congenital heart disease is present, use the 7000 code found in the miscellaneous section.