1 of 5

PERCEIVED RISK ADVISORY COMMITTE MEETING

REPORT

INTRODUCTION

*The first meeting of the Perceived Risk Advisory Committee was held February 24 and 25. The primary role of the Committee is to provide achieve and recommendations regarding the assessment of population risk perceptions and on the methodology to quantitf and analyze these estimates. The Committee represents a wide distribution of professional attributes. The agenda for the first meeting lacked detail in order for the committee to establish the directions of the meeting. It was hoped the Committee would be responsive in the development of future agenda,s project plans, data analyses and survey objectives.**

COMMITTEE STRUCTURE AND PURPOSE

The diversity of Committee member backgrounds was an advantage as different views on the tapics of risk perception were discussed. The structure of the meeting appeared to be conducive to an open exchange of ideas and productive dialogue.

It was felt an ethicist should be included on the committee roster. In addition, DOE should be advised in detail of activities and invited to attend.

The Committee will also be made aware of EHAP and mission, and the incorporation of the risk perception activities.

PLAN AND OBJECTIVES

The general plans and objectives were appropriate. However, future objectives and plans should provide more detailed information. It is the intent that detailed plans, objectives, strategies and activities be provided to the committee for review and comment before implementation. Also, a comprehensive literature review will be completed with a summary provided to the Committee. In addition, collected articles and references.

Is the measurement of risk perception an important component of population risk assessment?

- Risk perception may be better considered a part of the decision process along with risk assessment. I do not see risk perception as a component of risk assessment. Decision = f(Risk assessment, risk perception)

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* Italics indicate co-chairs' response to advisory meeting

- If DOE is to be a user of the service and product we are developing, then we need to identify who those specific customers are in DOE specifically.

- Feel the need to make it clear what similar programs have been done in the past, what they learned and the tie of the program to that post. Are we breaking new ground? Are we addressing questions not satisfied in the past? Similarly there is a need to show that methodology have been developed and their strengths/weaknesses. What is difficult whit this study?

- The perceived risk assessment is an important part of the environmental restoration effort. The work done by UC on risk assessment lending the cleanup standards must consider public opinion on the final results.

- We find the public very concerned with the site cleanup. The public wants the cleanup to background or near background levels. The cost of such cleanups are too high. The public needs to understand the relationship between cleanup levels, health risk and cost.

- I believe that research in the area of perceived risk perception is very important to the national agenda of site remediation. It should be pursued as you are now--applied to a wide variety of sites with some provision for site-specific work.

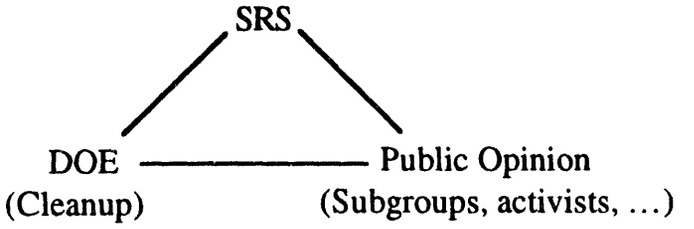
- Risk perception is an important aspect of risk management and is also an important part of drawing attention to a problem, real or perceived. I look at risk assessment as more of a quantitative tool such as hazard identification, dose-response, human exposure measurements and risk characterization. Risk perception is involved more in a quality assurance mode -- how well is the public perceiving the effectiveness of the actions? another aspect of risk perception could be an education process for the communities -- these could be local adult education, town meetings or others. Demonstrating the effectiveness of your program.

- Sell it to others: DOE, DOD, ATSDR.

- Bring black clergy into the process is extremely important. At the same time some education at or to (with) the teenagers could be beneficial.

- For future work, it would be helpful to know more about risk perception. Especially the development of an index of risk perception is important plus information about those aspects influence it.

- Suppose risk perception is developed in the following triangle:



  It has to be well defined where MUSC is situated. Is the area of the study: 1) Validating and describing or 2) Participating in the process of the development of risk perception?

- This has an impact on the study design: surveys or interaction study.

- Due to limited resources both in true and worry surveys with different questions might be preferred.

- When it comes to actually cleaning a site, many people are beginning to recognize that the cleanup cost is costing billions of dollars and many people are wondering if we can afford to clean up the sites. When we look at how clean a site should be, we are trying to balance the level cleaned to the public's perception of their health would be. The perceived risk is going to be the tricky one. The real contribution of this group would come from figuring out how to get the acceptable risk to zero.

- Can we go through and by factor and analysis can we come up with a quick response way so that when an incident occurs, you can do a telephone survey and have a sense of reaction and find out how you need to respond. You would respond very differently depending on what the answers are. Sort of like political poling in the risk industry. I think we need a proactive public health stance on risk.

- Risk perception is only part of the decision making process.

- I think that if we approach risk assessment from a purely technical view we may miss a part. Understanding what people are afraid of is a big part of the decision making process.

- Understanding the whole issue and trying to use the wisdom that is in the community can diffuse a lot of possible problems. I think it drives the scope of what points you are going to look at.

- How people benefit from the plant, their work, their livelihood effects the people's perception of the plant. People are mostly worried about their own community.

PILOT PROJECT RESULTS

The initial analysis of the pilot project results included an assessment by geographic area proximal tto he Savannah River Site and by race of the respondent. Future analyses will refine these assessments. Mechanisms to quantitf the responses will be developed. Analyses will be completed by socio-economic status and other population characteristics. In addition, analyses will be completed on a smaller geographic area than previously addressed. All analyses will be distributed to Committee for review and comment.

Is there a better way to present the results?
What aspects of the presentation are confusing and/or need additional clarity?

- I'd like to see data broken out in more detail for the 0-50 mile range, perhaps at 10 mile intervals, or perhaps by equal area.

- I favor presenting more of the data in line chart form rather than on bars.

- Suggest review of attached article that links educational lead to attitude. I'm sure that the 0-50 mile area is much more educated and urban that the other two ranges. (Said that groups were of equal education levels. I don't understand hoe that could be if the

phone calls were random in what clearly are urban areas near in and rural areas beyond 50 miles.

- Repeatedly the question comes up as to why we are doing this survey. What is the objective? There is a need to better define what we want to do, why and who will want to use this developed product.

- As others have indicated, at this meeting I needed more information on the project -- the big overall project and other aspects. We need to have time and information to grasp (or regrasp) the information. Where does this fit in? What are the goals? And also specifically, what do you want from us?

- The presentation was clear-cut to me. Summary slides at the end which capture as much data as possible would be helpful. Also the data could be explained by and education.

- I would prefer bar charts -- easier to read than the tandem charts.

- I believe the advisory committee recommended that additional correlation be worked out with the current data base. Such as:
  Urban risk perception
  Rural risk perception
  Education
  Economics
  Age

- Eliminate "toxic" from toxic chemicals

- If you present to community groups, you should start out with an overview of the SRC/SRP and the purposes of this study. The public will need to understand some basic concepts about risk. The public will need help understanding that everything has a risk.

- Stick with the framework of the study.
  What is EHAP?
  What kind of studies does it include?
  What place does your study have in this framework?

- What is the objective of the pilot study?
  To text a questionnaire?
  To the lay the basis for next study?

- Give information of cases, overall and subgroups.

- Reconsider the wording especially of those questions, where the answers are 50% yes and 50% no, 50th overall and in subgroups. (perhaps the participants couldn't get the point of the question)

- Reconsider the multiple choice questions, give room for more than one answer.

- For which kind of study do you think the data might be a good basis?

- I guess from a public health standpoint, I would look at the two communities separately. I would see it as a different plan and try to get people involved.

- I think the issue of controllability is very important. If people are perceiving it as something that is totally out of their control.

- Maybe adjusting it to urban or rural areas would make a difference. Urban perception may be very different.

- I think the wording of Toxic Chemical may have caused some problems. The way it's worded you almost have to agree with it.

- I would be inclined to think that by going right into questions on cancer, you are stacking the response because it shows that is the main focus of your survey.

- You may have to sacrifice some of your response rates to get a more accurate questionnaire. You will get a much higher response rate in rural areas that you will in urban areas because they immediately think you are selling something.

- I think taking some samples from this and talk to people in a smaller group -- in a focus group kind of session. I think we learn a lot more from focus groups if they are done correctly. What about the people who are within ten miles of the site or five miles for the site. What about the issue of minority people who live close to the site that don't have telephones.

- What you might do is take a look at the last high blood pressure survey that was done house to house.

- I think you would want to qualify economic questions to see how people feel about economic impact so that you can get an idea about people who work at the plant.

- Go back and operationalize the issues to find out what is important to know around the site. Find out what the people think they need to know about and around the sites.

- What you would really want to know is their perception of exposure to low dose radiation. I don't even know if they would know what that is. Did any of the questions deal with the dose question?

- We did a dose question and found that if exposed at all at any dose, people were concerned with it. I think you need some kind of experience base and relate it to like a chest x-ray or work-related exposure because what you are probably getting in the less than 50 miles you are getting a higher level of knowledge of what they may be exposed to.

- See if there is a threshold to see what levels are acceptable.

- It seems to me that your end product is two levels:
    1) What is their knowledge
    2) What is their attitude

- You need to ask a few short questions. They key knowledge questions that can tell knowledge or education and if they are informed or not informed. The trick is to look for sentinel questions. Part of risk management would be education the community to reduce the level of anxiety and increase the level of involvement.

- For those who answered that they have a greater chance of getting cancer, ask why do you think you have a greater chance of getting cancer.

- Can you tell what is perception and what is reality?

- Include age: Generation difference. Also, you might think about some open ended questions. ie: What have you heard or read? Another thing would be a hypothetical -- Where would you go to get info.? Needs refocus to define channels.

- You need more linkage. Ask questions about cancer and birth defects in family. Patterns of care seeking, patterns of information seeking. I think there has been an awful lot done on basic science -- how people perceive risk.

RECOMMENDATIONS FOR ADDITIONAL ANALYSES OF THE PILOT PROJECT DATA

- When we talk about developing a product that may impact the public at a specific site, there is good reason to bring "stakeholders" into the meeting. But., for the purpose of this group -- To develop a methodology for risk perception and how to employ is the desired focus. Suggest leaving stakeholder issues to the very large Crossroads Program at EHAP. A year down the road we can relook the desirability of bringing "stakeholder" and how they could act because of their often highly opinionated orientation.

- Recommend caution about becoming drown off into too much effort in focus groups and other gatherings of people like done on a very large scale basis by the Crossroads component of the EHAP effort. Use the output of Crossroads to color your program, but be careful to not try and be like Crossroads. That is a very expensive effort for the product received.

- Subgroup analysis especially closer circles than the first 50 miles.

- How men and women view risk.

- Can you correlate living close to the plant with "strong" reactions.

- Is the primary health concern "cancer"

- In general, a finer breakdown of the risks versus perceptions.

- Identify the parameters that are most sensitive for the public risk perception involuntary risk versus voluntary risk (worker).
  Living close to the plant
  Benefit vs. no benefit
  Educational levels
  Economic status
  Money -- effect of DOE paying millions of dollars to people living near the plant "presumed harmed"

- I think it would be interesting to explore why you are not seeing racial difference. It is the fact that they in fact feel less empowered and were more accepting of risk. You should be seeing difference there.

- I would really like to see a lot more done with what you have. I would try to get people thinking about what people are doing down here. If you are seeking money from the

government to support something, then getting something out there that looks meaningful is important. I would also think that if you are doing this for a customer called DOE, you should go out there and find out what they want. If you can study something and determine something, then you are of greater value. You've got something now that you could show as a sample and use it to say what do you need and what could we do to help you.

- I think as soon as you can get the public involved in this -- in a more than survey role -- the better.

- Early on you talked about wanting to have a risk perception center and establishing some expertise here and that is where the DOE comes to mind. They have nothing on risk perception right now and if you can step out and become a center that would be the thing to do.

- If you go to community groups where you go to provide them a service. You want them to go away feeling like they've been provided a service and not used and maybe that is where the focus groups would be better.

- I think you need to elaborate on the kinds of concerns that people have and then look at the different groups.

- I think you need to do more to develop a methodology for risk perception instead of studying differences between black and white. Let Crossroads do that.

- Need to focus on methodolgy and what it is we're trying to measure. Need a recognizable endpoint.

- Try to figure out hoe people view environmental hazards and when they determine the y are political, community health or medical problems. At what point do you go through what particular channel. Need a way to segment public response in a way that tells you how to go with it.

- Do a literature search. Compile list of individuals, institutions and funding sources who are doing similar research.

- Up river/down river might be another analysis.
- Look at what your own organization is doing an avoid duplication.

DISCUSSIONS REGARDING A PUBLIC ACCEPTABLE RISK

A "public acceptable risk level" will be considered with future survey parameters. However, the quantification needs considerable background research.

Is it possible to determine such an indicator?
What are the components of estimating a public acceptable risk level?
Would such an indicator by used in environmental remediation?

- Public acceptable risk can come about primarily through education and trust. Perhaps the best way to educate and earn the trust of the community is to bring one or two of them as early as possible and make them part of the team. This would be done on a case-by-case basis. We need to think more about this and what comprises it. This

factor would be extremely beneficial to remediation -- especially if the public buys into it.

- For determining the public acceptable risk I think that it may be initially useful to provide measurements of a toxicant in a sample of the potentially most highly exposed people. The subpopulation would be chosen by the community -- mayors, activists, church, school administrators, etc.). A laboratory would then measure the appropriate biomarker (if possible). These levels could be compared to levels or other data form a reference laboratory (we at CDC have a lot of reference data.)

- Recommend a specific effort to review the literature in some depth, identify the key publications, institutions and researcher/practitioner. Prepare a summary of what is the state of the art lessons learned, and what needs to be done next. With this basic and contact with the identified experts layout the indicator and the components.

- Environmental remediation should be the goal of the study, but first it is necessary to reach the goal of contributing a perceived risk index (which probably could be done by factor analysis). The questionnaire, likely modified, together with the results from other studies, is an instrument to conduct such an index.

- The risk level is the key to site remediation. Once the risk level is established, the cleanup levels can be calculated. This study has the potential of saving the DOE and the US taxpayer billions of dollars in cleanup costs. For example, at the current EPA risk level of 1×10^{-5} to 1×10^{-6} lifetime risk, the cleanup level at Mound for Pu would be 1 picocurie/g soil. An impossibly low level, at 1×10^{-5} annual risk the cleanup level is 100 picocuries/ g soil. Very achievable. Millions saved, no real health effects.

- The problem is exactly the same at Superfund sites. If you are going to involve the public early, they aren't going to agree on anything but the sites that have been clean up are the ones that have had more community involvement. The new Superfund legislation carries it over requiring states to set up community working groups structured to set up community involvement.

- We are a people who are willing to accept a vote and I think that someone needs to step up and say that we need a referendum on this sort of thin. Someone has to stand up to vote for some sort of solution and set some level of clean for the site.

- Take advantage of the fact that right now congress is very interested in a risk-based decision making process.

- Get feedback form DOE people. Talk to Heeb about inviting people and let invite people giving him the opportunity to be in the driver's seat.

- Be careful not changing character of meeting so that you are on display. Not show and tell for DOE. Maybe split up time and let advisory committee meet by themselves and with DOE. People are more on edge when the funding source is there.

- Try to come up with a definition of public acceptability. Talk to people at SRS about public content with levels. How do you know if the public is accepting?

- We're looking at risk perception and struggling with components. It may be more fruitful to come up with the components of acceptable risk rather than the end number.

- You need to construct an objective, develop a risk index and then use index to identify were risk is acceptable.

- Need to investigate how those two components interact. There's a lot of work on risk perception and that has some relationship t what is or is not acceptable, but I'm not sure what the relationship between those two is. People will clearly accept higher levels of risk if they perceive they will benefit economically. I don't think anyone has figured out how these two work together.

ADVISORY COMMITTEE AND NEXT MEETING RECOMMENDATIONS

Future survey protocols and objectives will be developed for review and comment from the Committee. These surveys will be well focused.

Two meetings per year are planned for the Committee. Dates for the meetings will be determined as task are completed in order to facilitate a more efficient meeting.

- When we hold our technical support group meetings, the room is packed with DOE people and what would be useful is to have another meeting and invite some the these DOE people. It would be a real eye opener for some of these guys because they don't think the way we do.

- The next meeting needs more structure. More specific proposals. It would keep us on track.

- Next meeting, review project (warm up time), then go over what you've done since the pervious meeting. Then state proposals to next step, giving us the opportunity to react to the proposals.

- Mail things out between meetings.

- Include a philosopher and ethicist. Ashford at MIT has done some environmental things. More useful to use someone with a more structured moral. Need structured review of who should be making the decision. (He also mentioned someone named Fletcher)

- Provide copies of articles and technical reviews on risk perception between meetings.

- Go to SRS and give them a preliminary. They might tell you what their problems are. I'm sure they've done plenty of surveys, but there may be some holes.

PERCEIVED RISK ADVISORY COMMITTEE MEETING

Sponsor:

Environmental Hazards Assessment Program
Medical University of South Carolina

Co-Chairs:

Daniel T. Lackland, DrPH, and
John B. Dunbar, DMD, DrPH
Department of Biometry and Epidemiology

For more information, please call (803) 792-2261.

CROSSROADS of HUMANITY

Topics to be Addressed

1. Additional analyses and considerations of the pilot project data.
2. Presentation of risk perception as related to population risk analysis assessment.
3. Components and concept of a population acceptable risk level.
4. Future sites and sample selection for Year 03 surveys. (Considerations: more sites vs. more respondents at one site.)

Agenda

Thursday, February 24 • Lodge Alley Inn

8:45 - 9:15 am	Coffee
9:15 - 9:30 am	Welcome and Introductions
9:30 - 10:15 am	Review of Plan and Objectives
10:15 - 10:30 am	Coffee Break
10:30 - Noon	Review of Pilot Project Methodology, Questionnaire and Results
Noon - 1:00 pm	Lunch and Discussions
1:00 - 2:30 pm	Recommendations for Additional Analyses of Pilot Project Data
2:30 - 2:45 pm	Break
2:45 - 4:30 pm	Discussion and Recommendations Regarding the Determinants of a "Public Acceptable Level" Determined From Population Assessment
4:30 pm	Adjourn
5:45 pm	Pick-up at Lodge Alley Inn
6:00 - 7:30 pm	Reception at Wickliffe House
7:30 pm	Return to Lodge Alley Inn
Dinner on own	

Friday, February 25 • Lodge Alley Inn

8:30 - 8:45 am	Coffee
8:45 - Noon	Discussions on Year 03 Activities, Future Survey Sites, Modifications of Methodology and Instrument, and Sample Selection
Noon	Adjourn

Introduction

Risk perception is an important consideration in environmental restoration and cleanup standards as well as being a key component of risk assessment. The quantification of perceived risks, risk awareness and knowledge of health hazards is critical to the determination of public-acceptable levels of environmental contamination. The development and implementation of methodologies are necessary preludes to any comprehensive environmental hazard and risk assessment program.

Goals, Objectives & Strategies

GOAL: *To develop, implement and maintain a comprehensive environmental risk perception assessment center and methodology, capable of rapid ascertainment evaluation and analyses of population data.* This program is designed to be a major resource for Department of Energy sites as well as other groups involved in the decision process for environmental remediation and restoration. Furthermore, the project will provide timely feedback of community and population-based findings to concerned parties, including the Crossroads and risk assessment programs.

OBJECTIVES:

- To develop methodology for the measurement of knowledge, awareness and attitudes with regards to environmental hazards risks to human health.
- To quantify these measures and construct a perceived risk index.
- To estimate levels of acceptable risk in the population.

STRATEGIES:

- Inventory of existing perceived risk assessment programs.
- Assessment of methodologies used to incorporate risk perception in decision making.
- Comprehensive review of literature on risk perception.
- Development of population pilot project.
- Development of an advisory committee.

Perceived Risk Advisory Committee

Roy E. Eckart, Ph.D., is Professor of Nuclear Engineering and Head of the Department of Mechanical, Industrial and Nuclear Engineering at the University of Cincinnati. Dr. Eckart's fields of special interest include radiological engineering, radiological environmental assessment, operational health physics and risk assessment.

Bernd Grosche, Ph.D., is the head of the Epidemiology and Statistics unit for the Institute for Radiation Hygiene at the Federal Office of Radiation Protection in Oberschlei Bheim, Germany. He has studied the health effects of radiation exposure for more than 10 years and has conducted research on such topics as "Incidence of Leukemia in Bavaria," and "Pregnancy and Birth Outcome in Germany after Chernobyl." Dr. Grosche holds a bachelor's degree in sociology from the University of Hamburg and is certified in epidemiology by the Deutsche Gesellschaft fur Medizinische Dokumentation, Informatik und Statistik.

Clark W. Heath, Jr., M.D., is Vice President of Epidemiology and Statistics for the American Cancer Society, a position he has held since 1988. He is a Clinical Professor of Community Health at the Emory University School of Public Health and is certified by the American Board of Preventive Medicine. Dr. Heath is a member of the American Association for Cancer Research and the American Association for the Advancement of Science. He is currently serving on the Committee to Study the Mortality of Military Personnel Present at Atmospheric Tests of Nuclear Weapons for the National Academy of Sciences. Dr. Heath holds his M.D. from Johns Hopkins University School of Medicine in Baltimore, MD.

Max R. Lum, Ed.D., is responsible for the Agency for Toxic Substances and Disease Registry's (ATSDR) initiatives in community and health professions education. He is chairman of ATSDR's Risk Communication Committee and project director of two recent guidebooks on risk communication. Dr. Lum has published numerous articles related to health education and risk communication and has lectured extensively on the subject. He received a bachelor's degree from the University of Maryland, and a master's degree in Public Administration and Doctorate in Medical Education from the University of Southern California.

David McCallum, Ph.D., is Principal of Focus Group, a risk communication, health and environmental management services organization in Washington, DC. Dr. McCallum conducts research on risk assessment and risk communication issues and is a consultant in communication strategy development and training for industry and government. He is currently an Adjunct Professor of Public Health at Columbia University. He has been a consultant for the EPA, the FDA and ATSDR. Dr. McCallum speaks regularly at meetings and workshops and has published many articles on risk communication.

Larry L. Needham, Ph.D., is Chief of the Toxicology Branch for the Environmental Health Laboratory Sciences Division, National Center for Environmental Health at the Centers for Disease Control and Prevention. Dr. Needham identifies and prioritizes studies involving human exposure to environmental organic toxicants and gives administrative direction to over 40 professionals in his department. He works in close collaboration with other federal, state and international scientists and administrators to improve the diagnosis, treatment and prevention of exposure to organic toxicants. He is frequently asked to serve as a spokesperson on exposure to organic toxicants before White House committees, staffs of Congress, scientific delegations and peer review panels. Dr. Needham holds a Ph.D. in organic chemistry from the University of Georgia.

Patrick M. O'Neil, Ph.D., is an Associate Professor and the Director of the Weight Management Center for the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina. Dr. O'Neil is the Vice Chairman of the Board of Examiners in Psychology for the state of South Carolina and has published a column on weight control in the Charleston *Post and Courier* for the past six years. He is a member of the American Psychology Association, the Association for the Advancement of Behavior Therapy, and the National Council Against Health Fraud. Dr. O'Neil holds a B.S. from Louisiana State University and a Ph.D. in Clinical Psychology from the University of Georgia.

Todd D. Stong, Ph.D., is Environmental Programs Advisor for Coleman Research Corporation in Fairfax, VA. With 11 years of research and development direction experience, preceded by 10 years of large-scale engineering management, Dr. Stong currently provides various technical directions for Department of Energy and Environmental Protection Agency programs. Among his accomplishments are: institution of consistency standards for the SDIO program and initiation of the first large-scale removal of PCB transformer oil in Germany. Dr. Stong holds bachelors' degrees in Engineering (U.S. Military Academy) and Electrical Engineering (Purdue University). He holds master's and doctoral degrees in Civil Engineering from Purdue and the University of New Mexico, respectively.

Jeffrey A. Lybarger, M.D., is the Director of the Division of Health Studies for the Agency for Toxic Substances and Disease Registry. He is a member of the International Society for Environmental Epidemiology, the Society for Occupational and Environmental Health, and the American Public Health Association. Dr. Lybarger is certified by the American Board of Preventive Medicine in occupational and preventive medicine and holds a B.A. and a M.D. from Southern Illinois University, and an M.S. in Environmental Health from the University of Cincinnati's College of Medicine.

PERCEIVED RISKS AND KNOWLEDGE ASSESSMENT SURVEY

FIPS STATE CODE	STRATUM CODE	PSU NUMBER	RECORD NUMBER	DATE OF INTERVIEW MM DD YY	INTERVIEWER ID
☐☐	☐	☐☐☐☐☐	☐	☐☐☐☐☐☐	☐☐

HELLO. I'm (NAME OF INTERVIEWER) Calling for the Survey Research Center. We're doing a study of the health opinions and concerns of residents of the Southeastern United States.

Your number has been chosen randomly to be included in the study, and we would like to ask some questions about your ideas of things which may affect health.

1. Is this ☐☐☐ ☐☐☐ ☐☐ YES -> GO TO QUESTION 2

NO -> Thank you very much, but I seem to have dialed the wrong number. It is possible that your number may be called at a later time. STOP.

2. Is this a private residence? YES -> GO TO PAGE 2.

NO -> Thank you very much, but we are only interviewing in private residences. STOP.

Refusal Information

FINAL DISPOSITION OF TELEPHONE CALL. ☐☐

01- Completed Interview
02- Refused Interview
03- Non-working Number
04- No Answer (multiple tries)
05- Business Phone
06- No Eligible Respondent at this number
07- No Eligible Respondent could be reached during time period
08- Language barrier prevented completion of interview
09- Interview terminated within questionnaire
10- Line busy (multiple tries)
11- Selected respondent unable to respond because of physical or mental impairment

Edited by: _____ Date: _____

Our study requires that we interview only one person who lives in your household.

1. How many members of your household, including yourself, are 18 years of age or older? ☐

IF ONE PERSON HOUSEHOLD
GO TO "ALL RESPONDENTS"

---

2. How many are men and how many are women? Men ☐ Women ☐

3. Who is the oldest man/woman presently lives in this household?

4. Who is the next oldest man/woman presently lives in this household?

INTERVIEWER ORDER OF LISTING IS ALL MEN FIRST, OLDEST TO YOUNGEST, THEN ALL WOMEN, OLDEST TO YOUNGEST.

Resident Number	Name/Relationship	LAST DIGIT OF TELEPHONE # 0	1	2	3	4	5	6	7	8	9	Resident Number
1		1	1	1	1	1	1	1	1	1	1	1
2		2	1	2	1	2	1	2	1	2	1	2
3		3	1	2	3	1	2	3	1	2	X	3
4		1	2	3	4	1	2	3	4	X	X	4
5		2	3	4	5	1	2	3	4	5	1	5
6		5	6	1	2	3	4	X	X	X	X	6
7		2	3	4	5	6	7	1	X	X	X	7
8		8	1	2	3	4	5	6	7	X	X	8

The person in your household that I need to speak with is _____

INTERVIEWER: IF RESPONDENT IS NOT HOME, TRY TO ARRANGE TIME FOR CALLBACK

_____ Date _____ Time

IF SCREENING WAS NOT DONE WITH RESPONDENT

Hello. I'm (NAME OF INTERVIEWER) calling for the Survey Research Center. I'm a member of a special research team. We're doing a study of residents in the Southeastern United States regarding their health concerns. You have been randomly chosen to be included in the study from among the adult members of your household.

ALL RESPONDENTS

The interview will take about 10 minutes or perhaps a little less and all the information obtained in this study will be confidential.

Your name will not be used, but your responses will be grouped together with information from others participating in the study.

Of course, your part is voluntary and you can refuse to answer any questions or even end this interview anytime you like. ....

ATTITUDE

1. The first questions involve word association. For example, when I mention the word baseball, you might think of the World Series, summertime, hot dogs, or the Atlanta Braves. We are interested in the first three thoughts that come to your mind when you hear Savannah River Site.

   What is your first thought or image that comes to mind? _____

   _____

   Second thought or image? _____

   _____

   Third thought or image? _____

   _____

KNOWLEDGE

2. In your opinion, do people in your community have a greater chance, less chance, or equal chance of getting cancer compared with other people in the state?

Greater Chance	1	
Less Chance	2	(Go to Question 5)
Same Chance	3	(Go to Question 6)
Don't Know	7	(Go to Question 6)
Refused	9	(Go to Question 6)

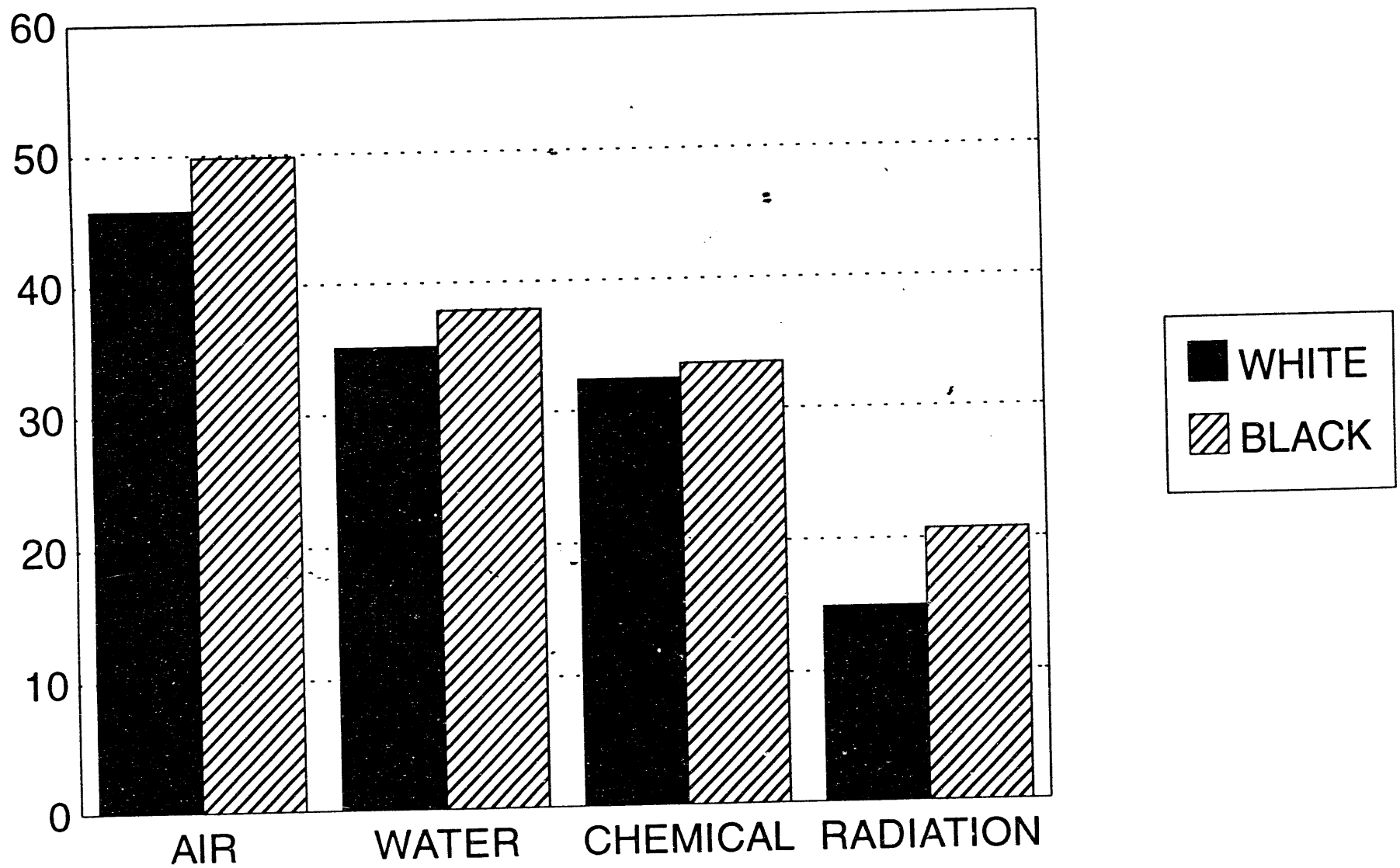
3. (IF GREATER CHANCE) Why do you think people in your community are more likely to get cancer?

Pollution	1	
Genetics	2	(Go to Question 6)
Tobacco Products Use	3	(Go to Question 6)
Eating Habits	4	(Go to Question 6)
Occupation	5	(Go to Question 6)
Other _____	6	(Go to Question 6)
Don't Know	7	(Go to Question 6)
Refused	9	(Go to Question 6)

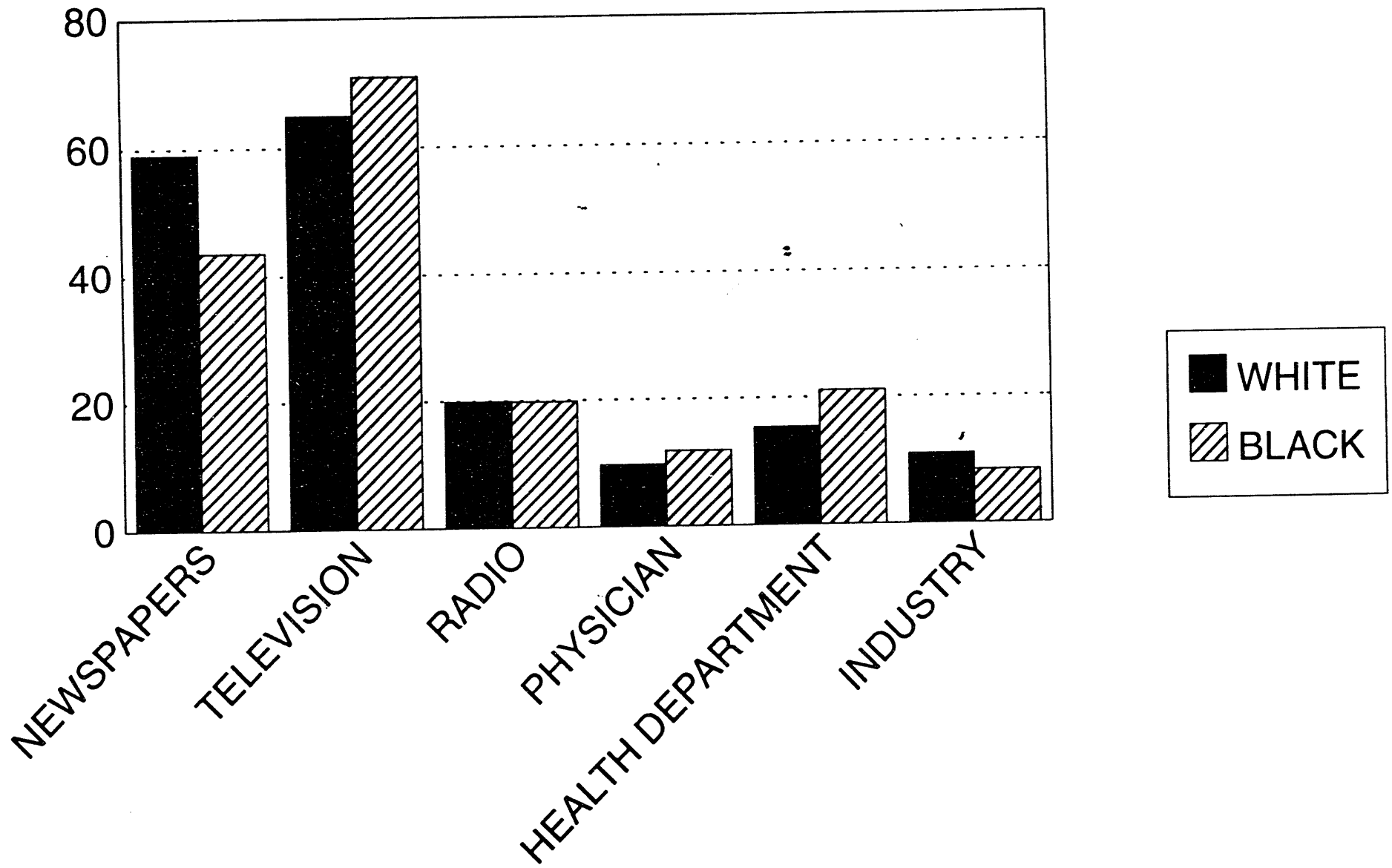
TYPE OF CANCER MOST PREVALENT IN COMMUNITY - RESPONDENT OPINION

	WHITE	BLACK
LUNG	44.4%	47.6%
BREAST	13.0%	14.1%
PROSTATE	4.1%	5.7%
LEUKEMIA	3.5%	4.0%
COLO-RECTAL	7.3%	6.2%
OTHER	11.7%	7.5%

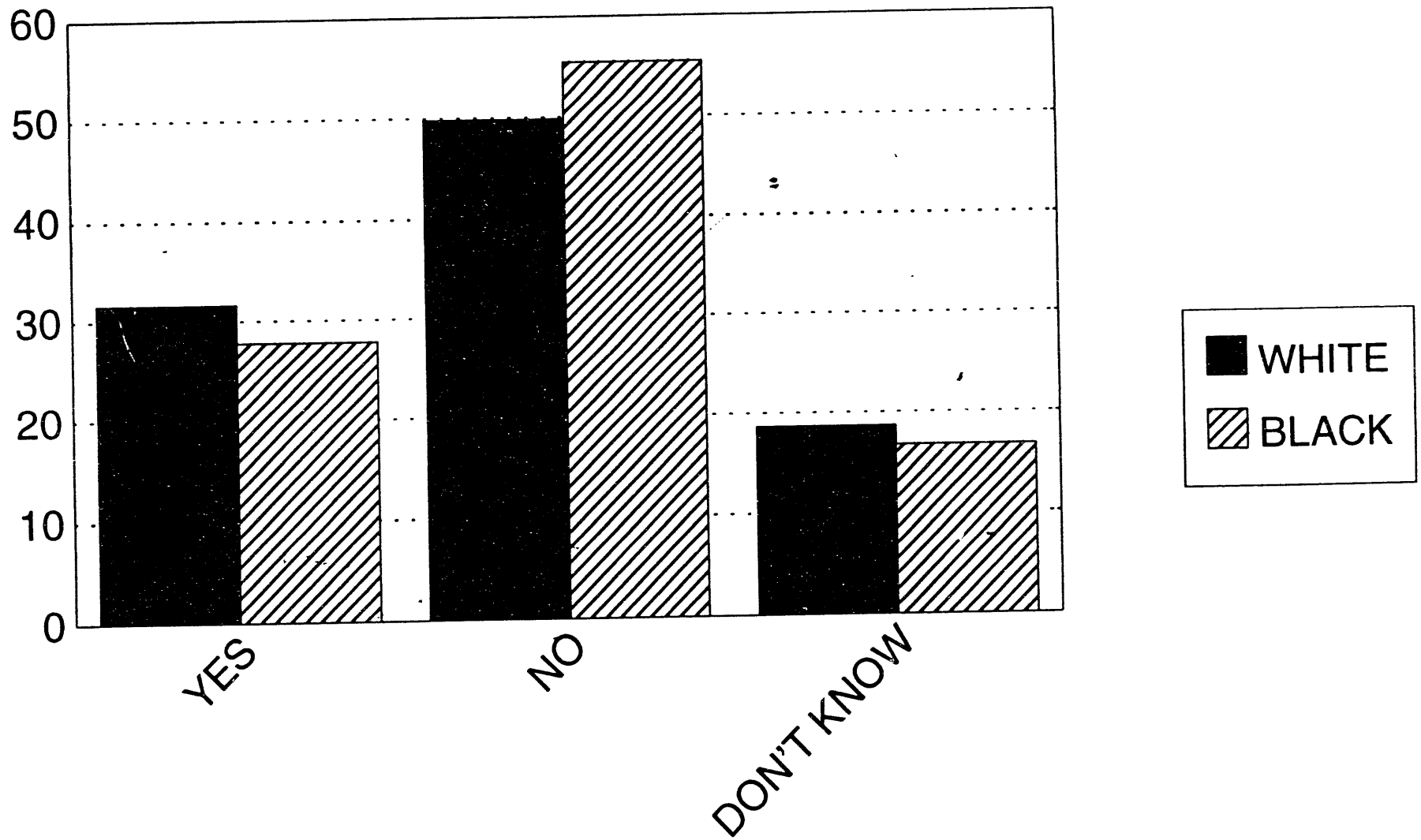
OPINION THAT POLLUTION EXISTS IN COMMUNITY THAT IS HARMFUL TO ONE'S HEALTH



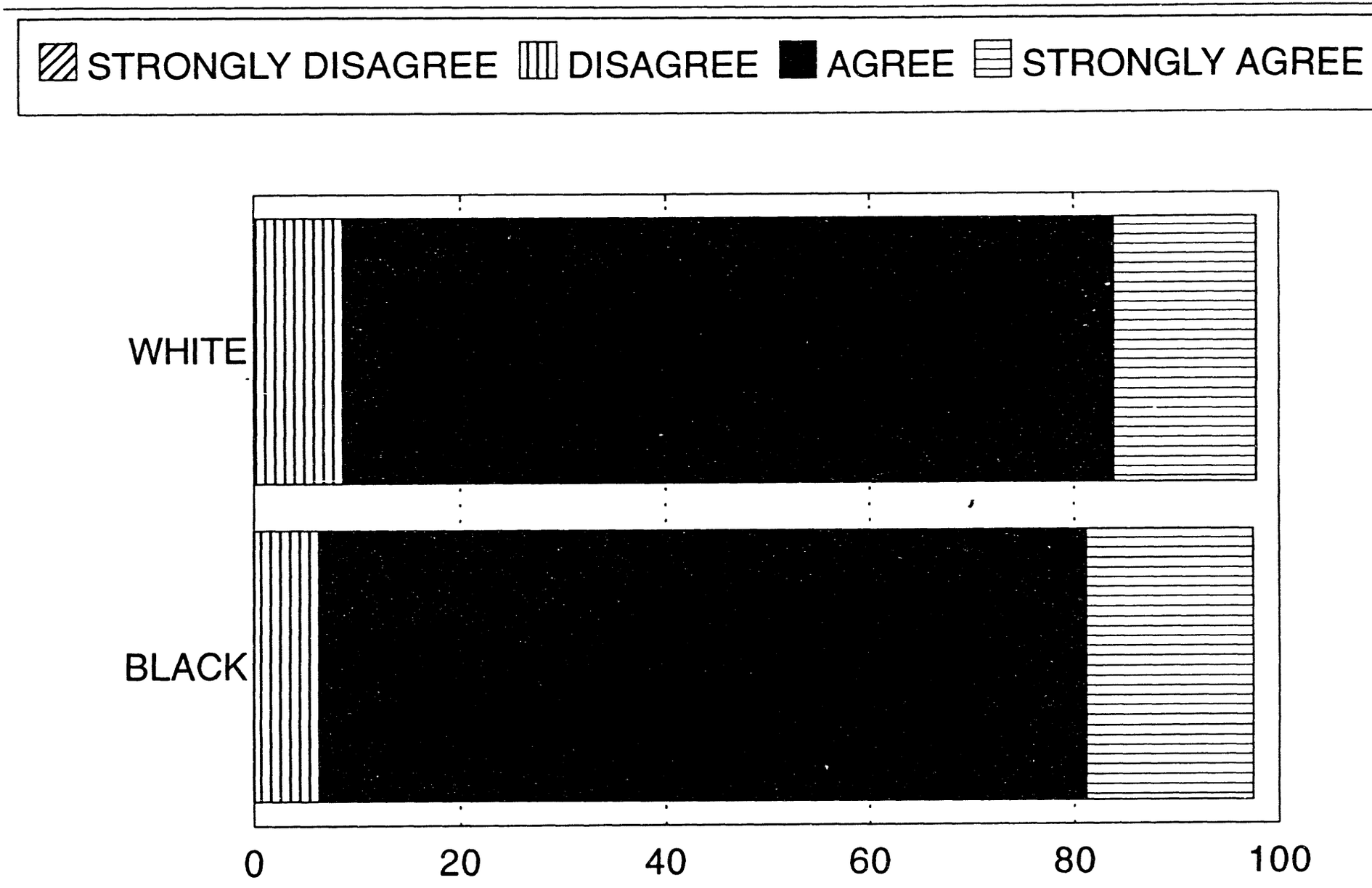
SOURCE OF INFORMATION REGARDING POLLUTION



DO YOU FEEL THERE IS ENOUGH STUDY OF POLLUTION BEING DONE IN YOUR COMMUNITY

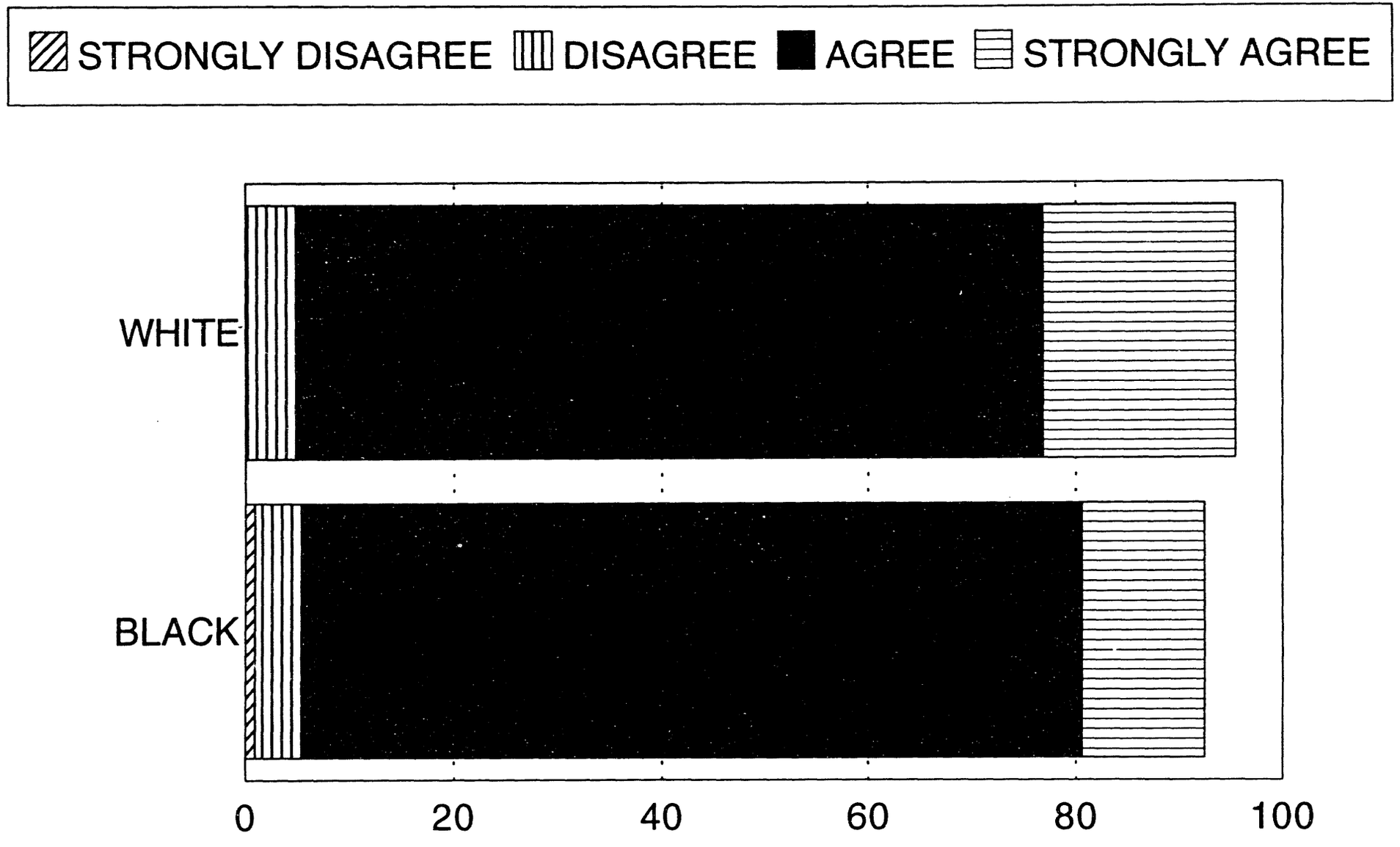


THERE IS ALWAYS A RISK WHEN USING CHEMICALS



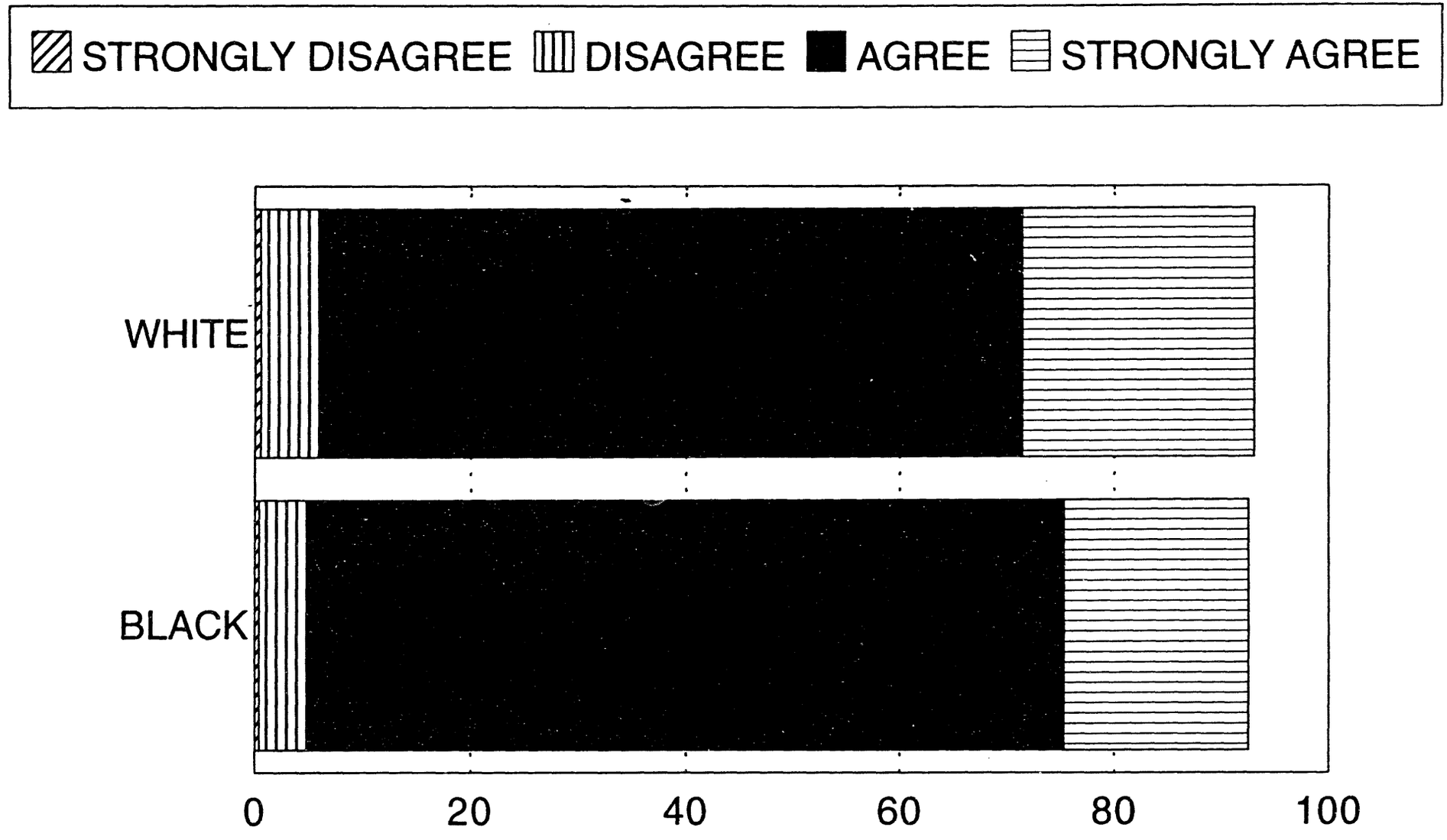
P-VALUE NOT SIGNIFICANT

IF EXPOSED TO A TOXIC CHEMICAL, LIKELY TO SUFFER ADVERSE HEALTH EFFECTS



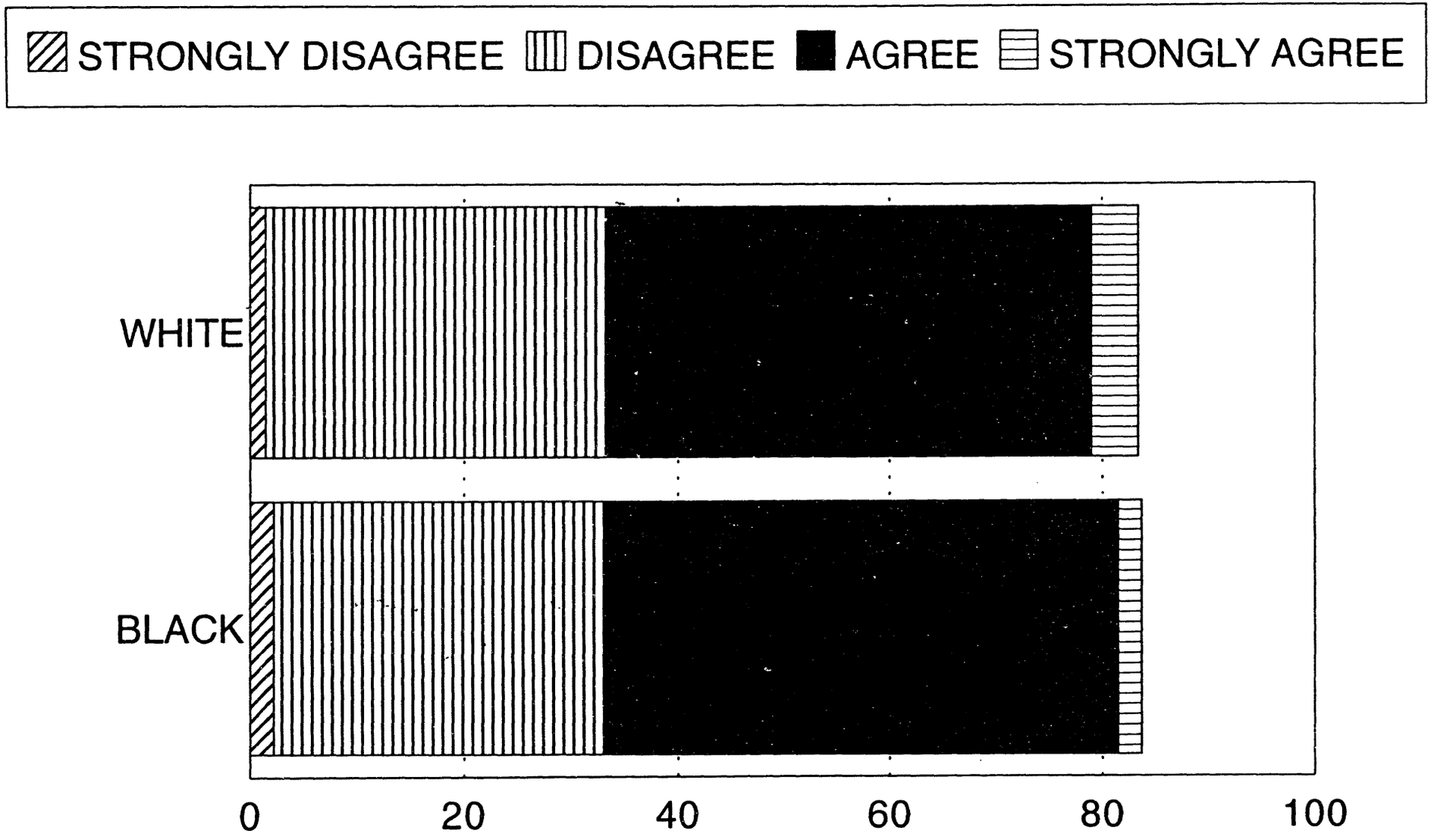
P-VALUE NOT SIGNIFICANT

IF EXPOSED TO RADIATION, LIKELY TO SUFFER ADVERSE HEALTH EFFECTS



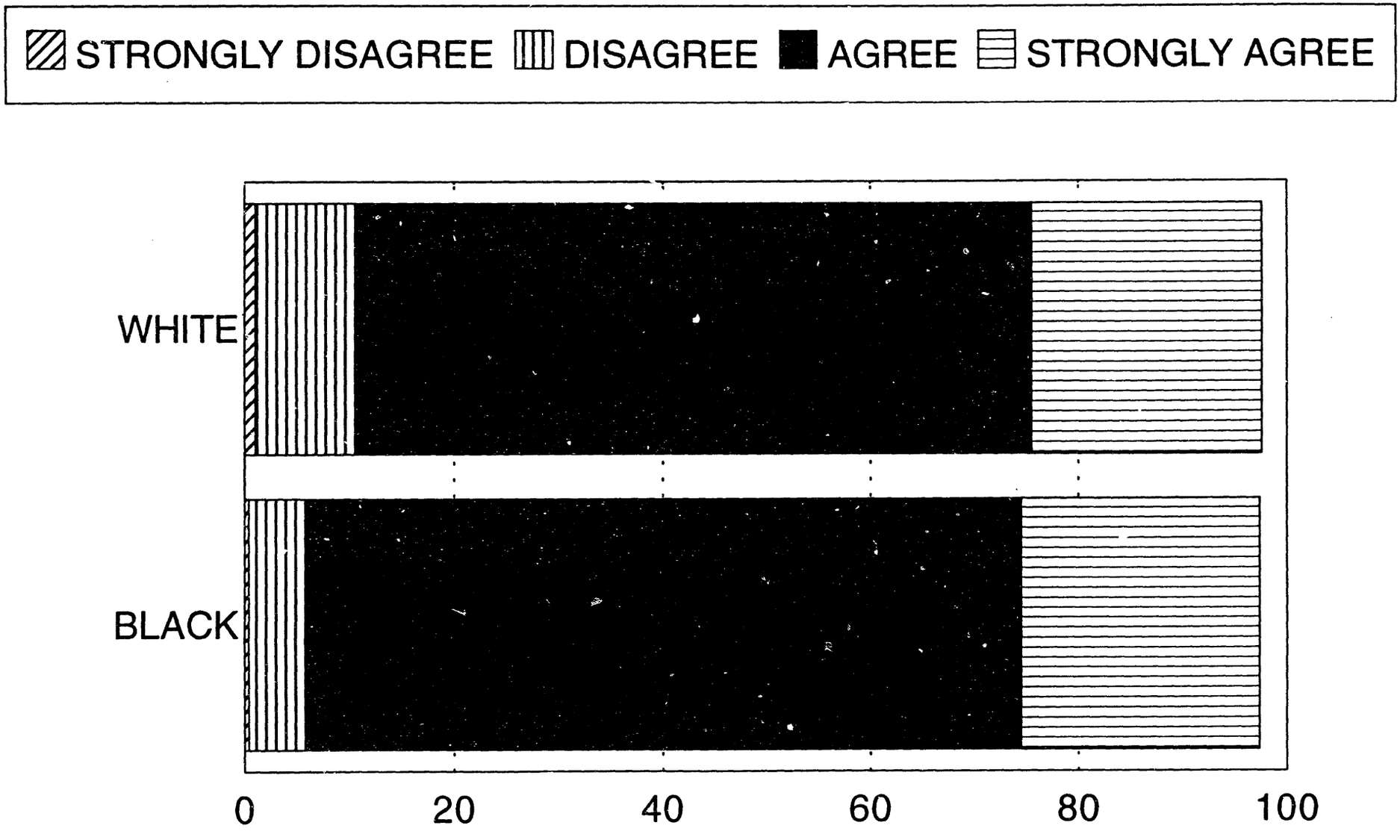
P-VALUE NOT SIGNIFICANT

THE WAY AN ANIMAL REACTS TO A CHEMICAL IS A RELIABLE PREDICTOR FOR HUMANS



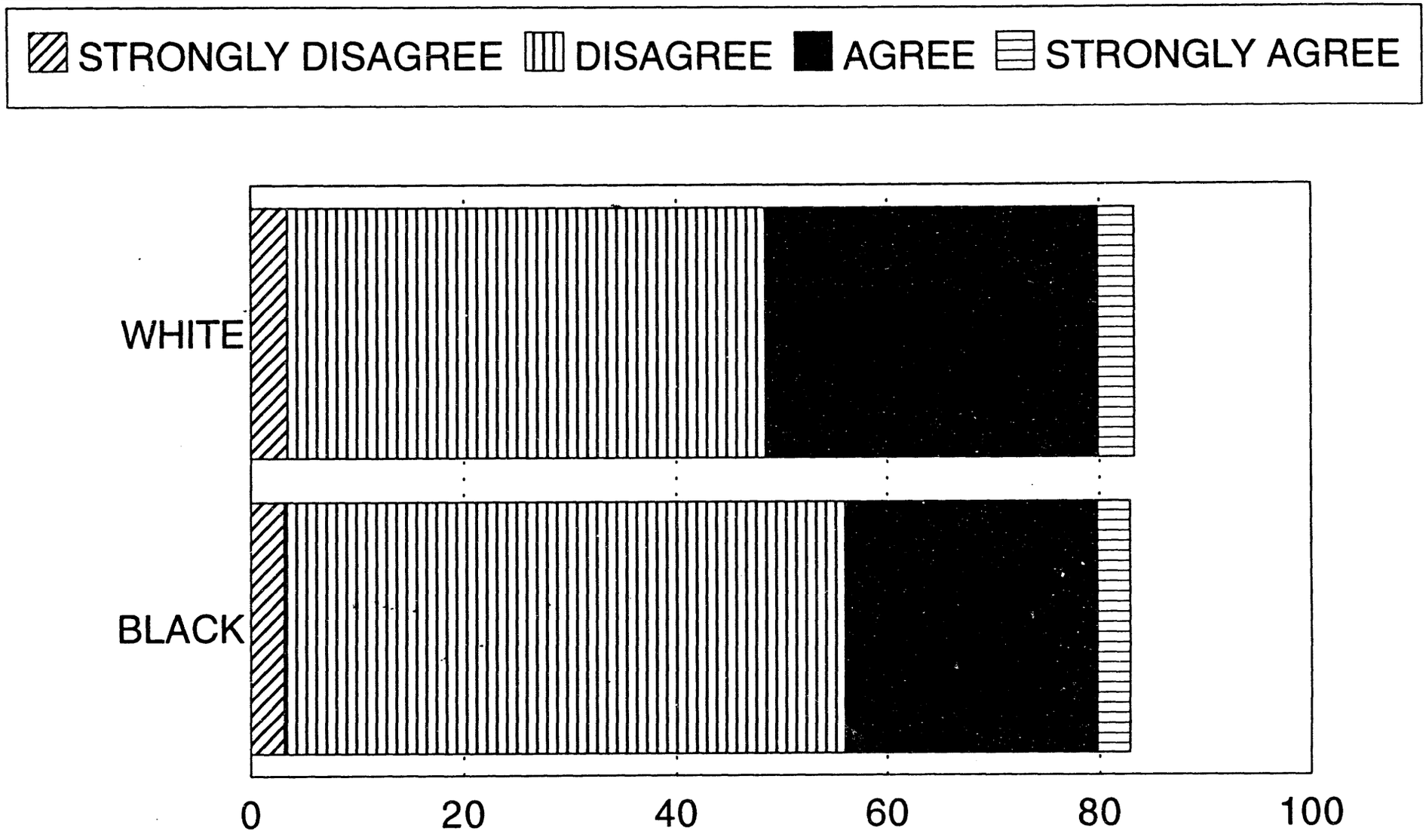
P-VALUE NOT SIGNIFICANT

THE LAND, AIR, AND WATER AROUND US ARE MORE CONTAMINATED NOW THAN EVER BEFORE



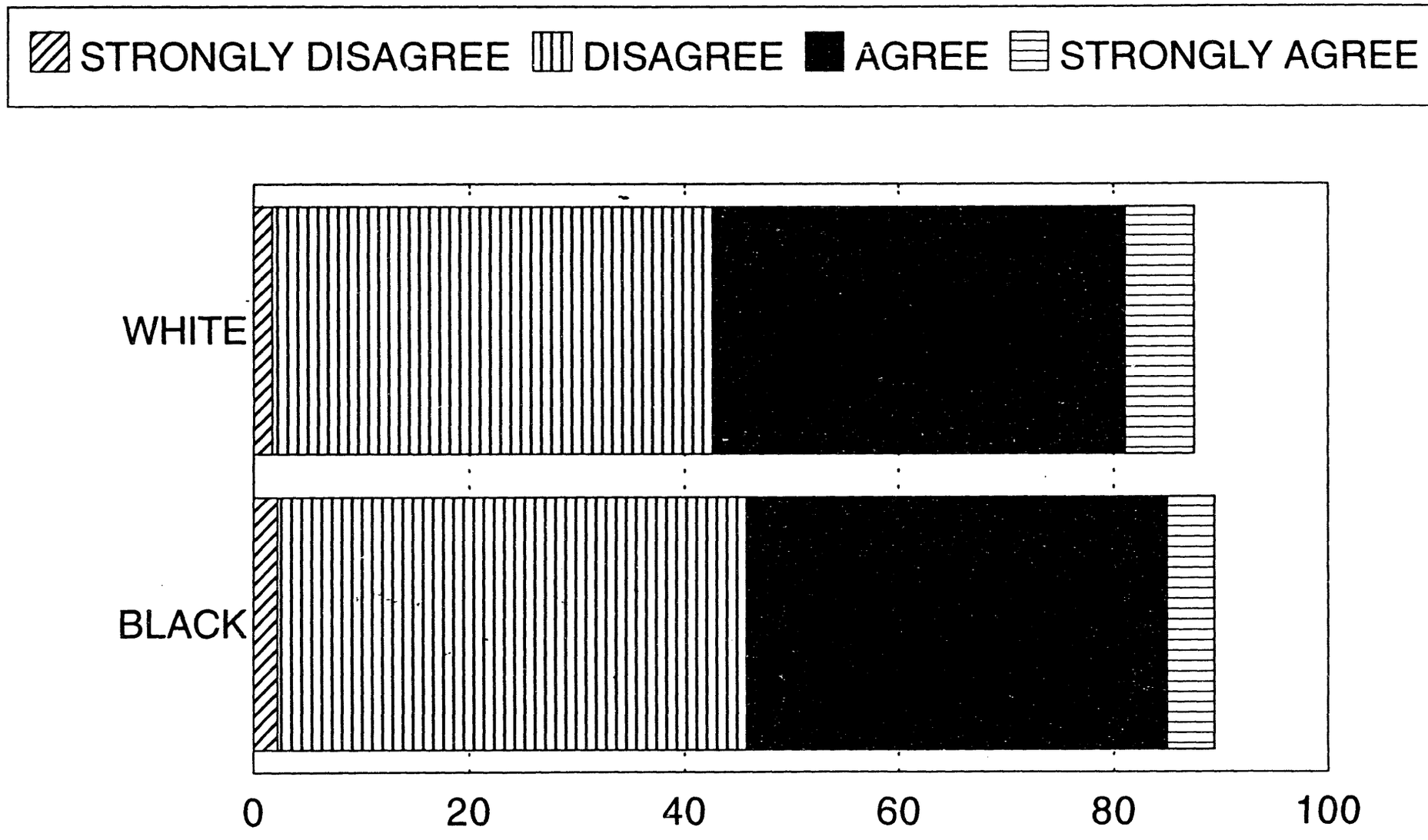
P-VALUE < .1

USE OF CHEMICALS HAS IMPROVED OUR HEALTH MORE THAN IT HAS HARMED



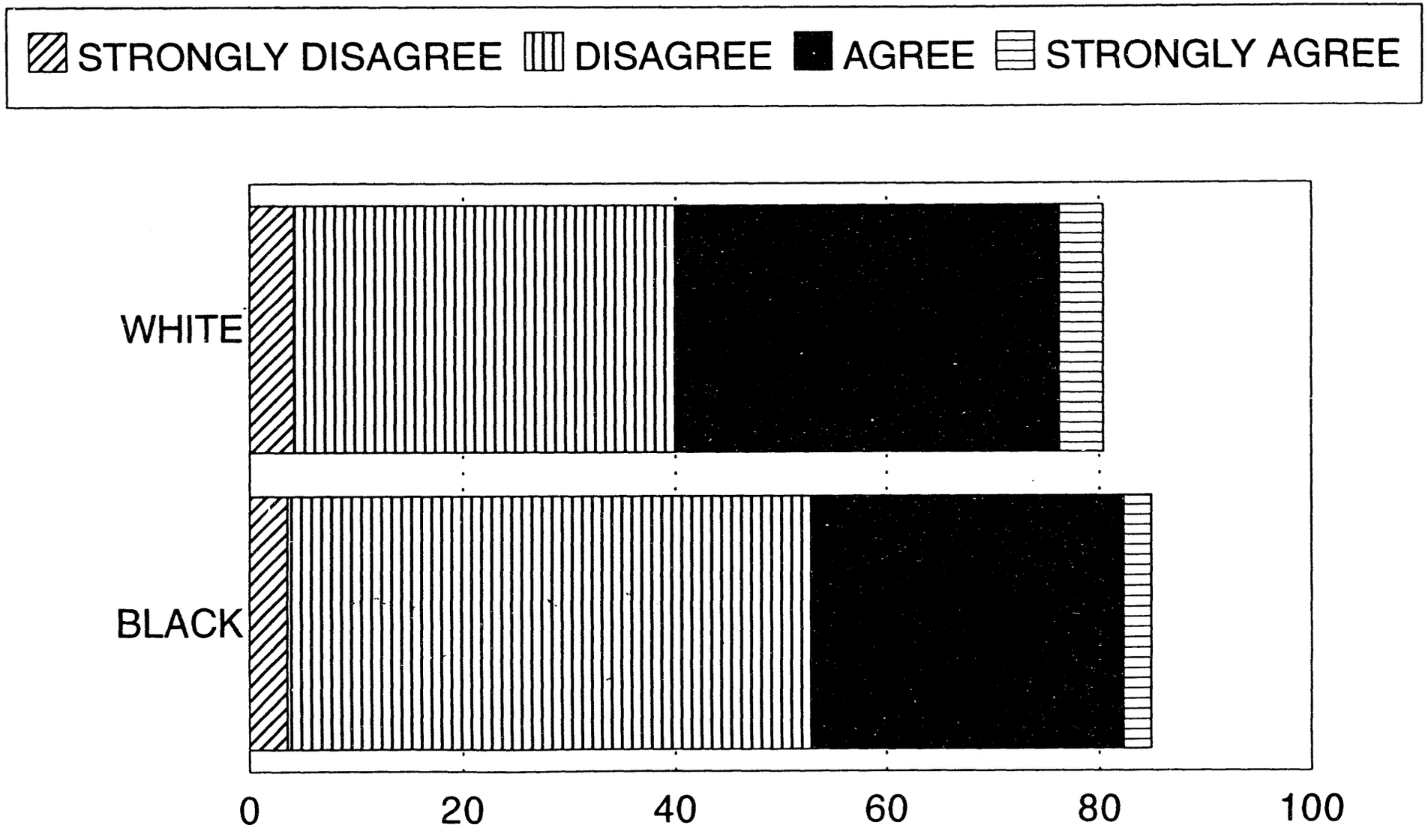
P-VALUE NOT SIGNIFICANT

IT CAN NEVER BE TOO EXPENSIVE TO REDUCE THE RISKS ASSOCIATED WITH CHEMICALS



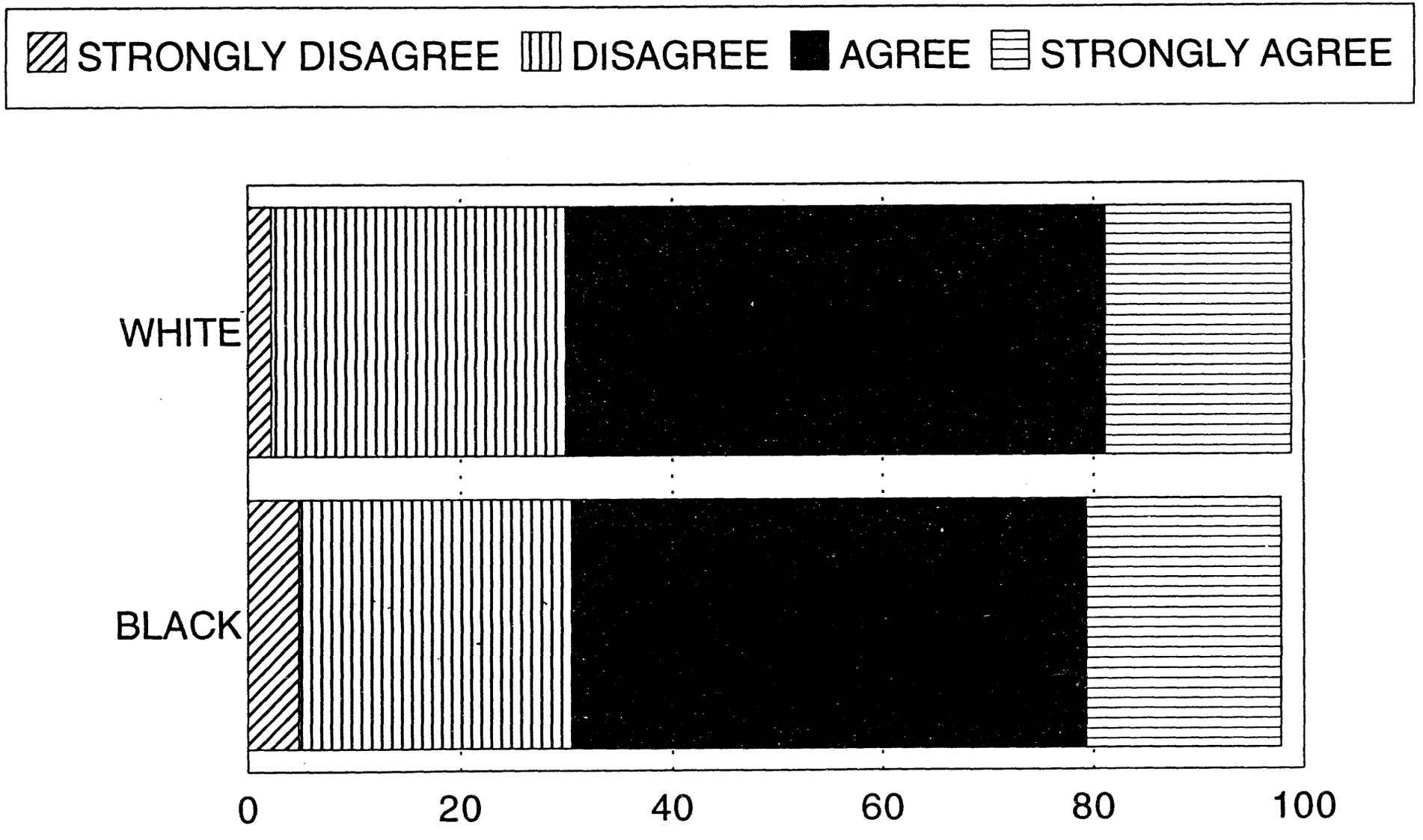
P-VALUE NOT SIGNIFICANT

USE OF RADIATION HAS IMPROVED OUR HEALTH MORE THAN IT HAS HARMED



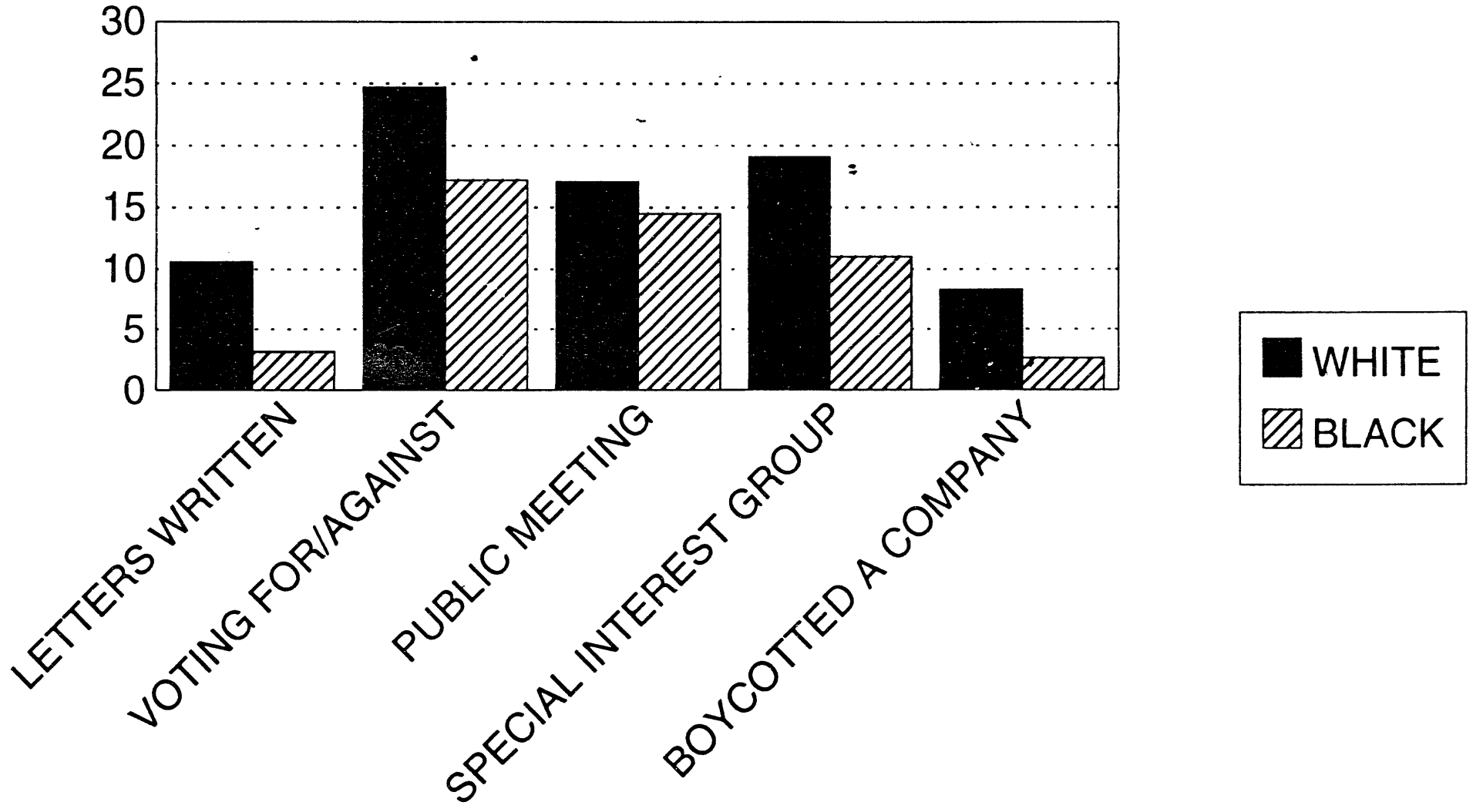
P-VALUE NOT SIGNIFICANT

SHOULD KNOW AS MUCH AS POSSIBLE ABOUT THE CHEMICALS IN THE ENVIRONMENT



P-VALUE NOT SIGNIFICANT

ACTIONS TAKEN TO EXPRESS VIEWS OR CONCERNS REGARDING POLLUTION



SECTION

Plan and Objectives

Is the measurement of risk perception an important component of population risk assessment?

NOTES

Pilot Project Results

Is there a better way to present the results?

What aspects of the presentation are confusing and/or need additional clarity?

NOTES

Recommendations for Additional Analyses of the Pilot Project Data

NOTES

Discussions Regarding a Public Acceptable Risk

Is it possible to determine such an indicator?

What are the components of estimating a public acceptable risk level?

Would such an indicator be used in environmental remediation?

NOTES

Future Survey Considerations

What sites are recommended to be studied?

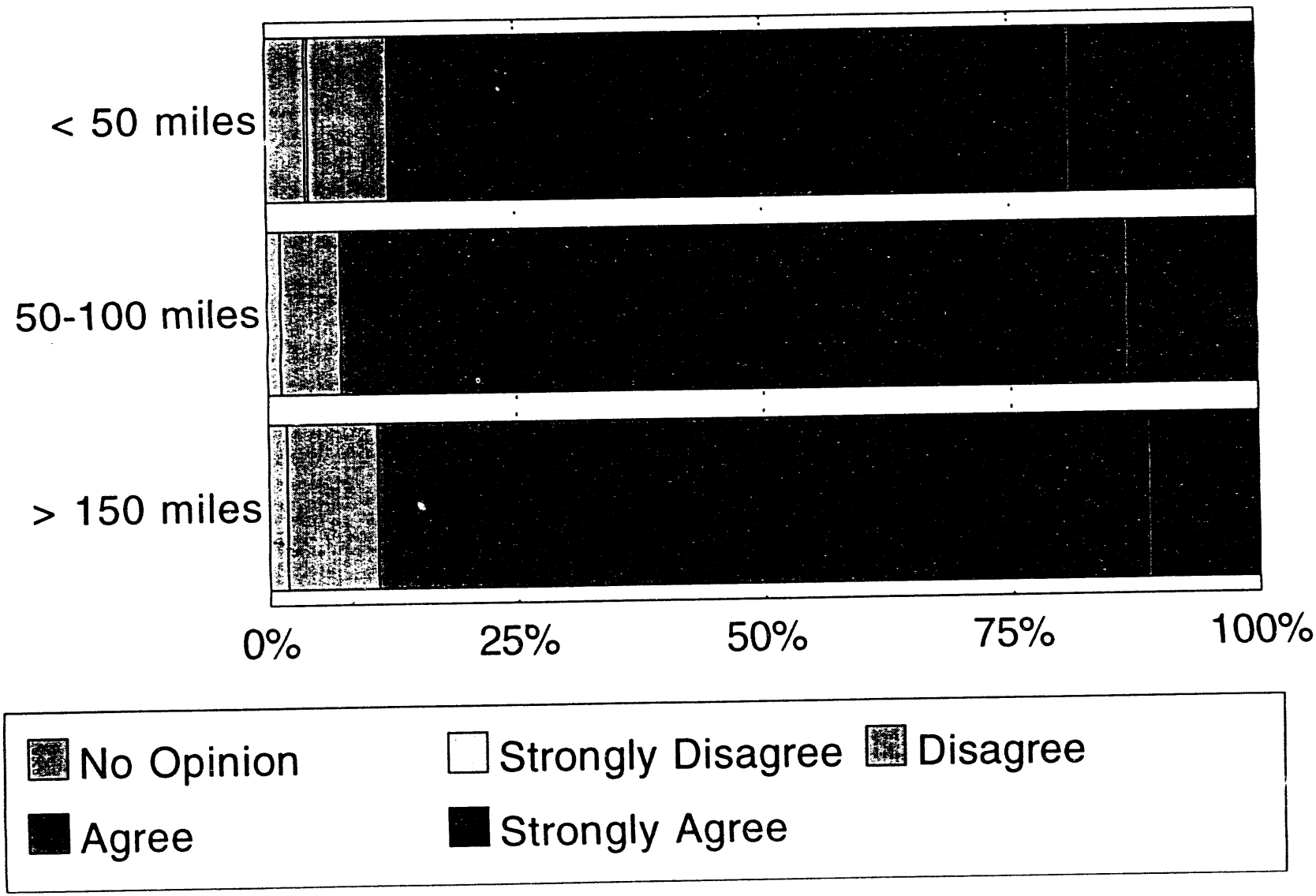
What are the recommended modifications in the instrument and protocol?

Should we do more sites or more respondents at each site?

Should the sample be drawn proximal to the site?

Should the major objectives remain the estimation of risk perception and awareness and the calculation of a public acceptable risk level?

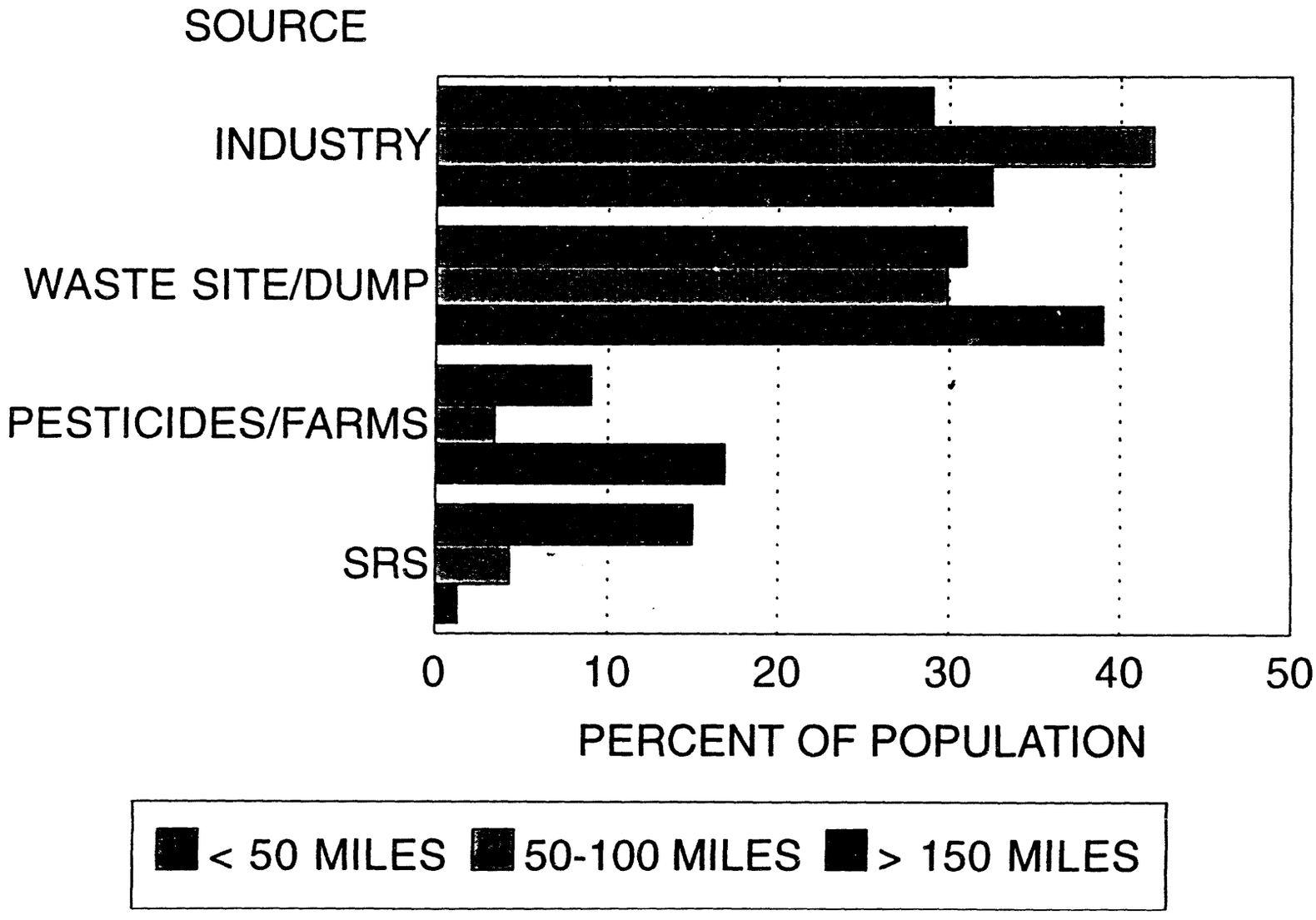
THERE IS ALWAYS A RISK WHEN USING CHEMICALS



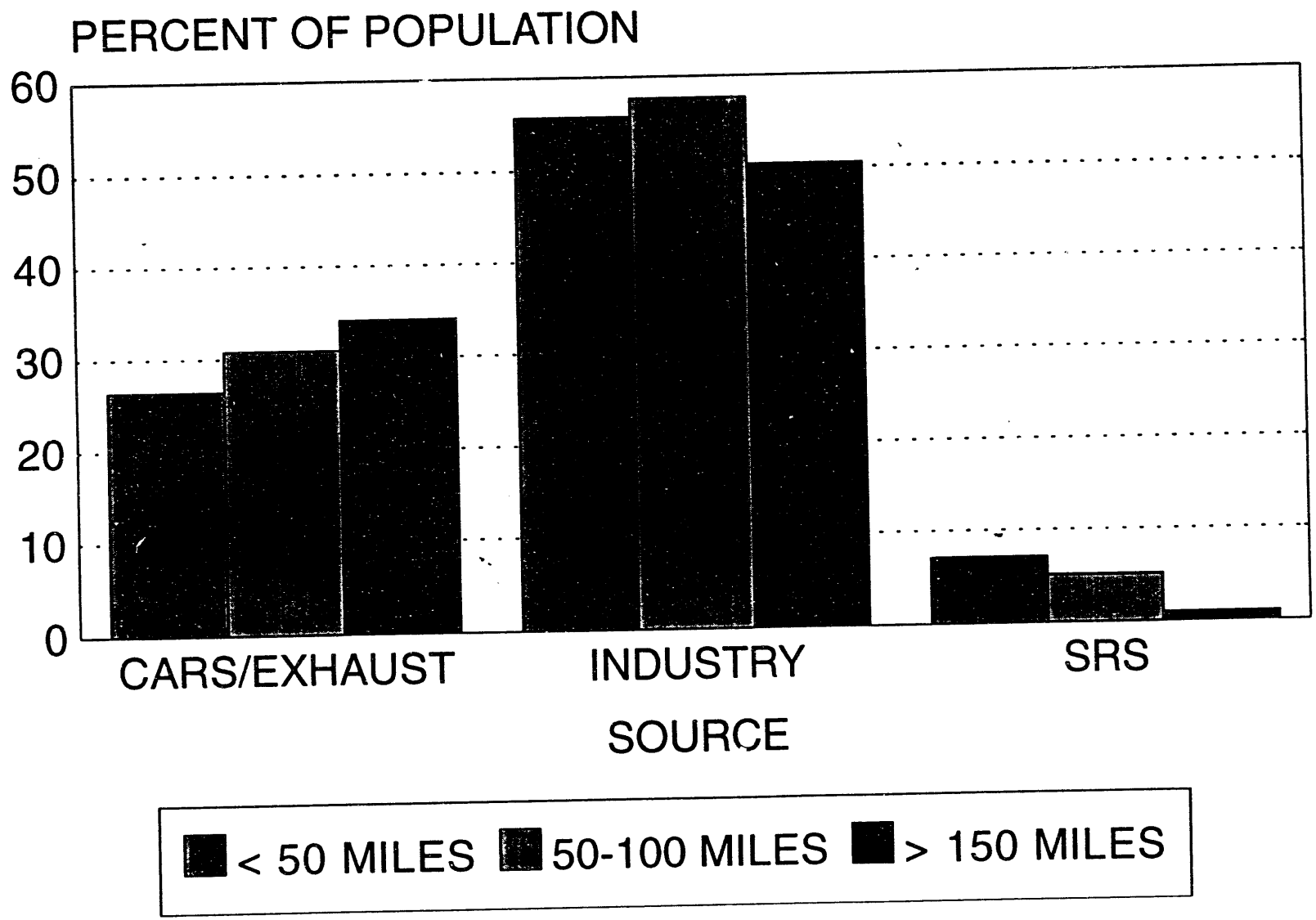
MAJOR RISK FACTOR ASSOCIATED WITH HEART DISEASE AND STROKE

	< 50 MILES	50-100 MILES	> 150 MILES
DIET	31.3%	34.7%	25.9%
HIGH BLOOD PRESSURE	16.1%	15.3%	22.7%
LACK OF EXERCISE	4.5%	6.0%	4.5%
HIGH CHOLESTEROL	5.5%	6.7%	7.3%
CIGARETTE SMOKING	18.1%	17.0%	17.3%
STRESS	17.1%	17.0%	17.7%

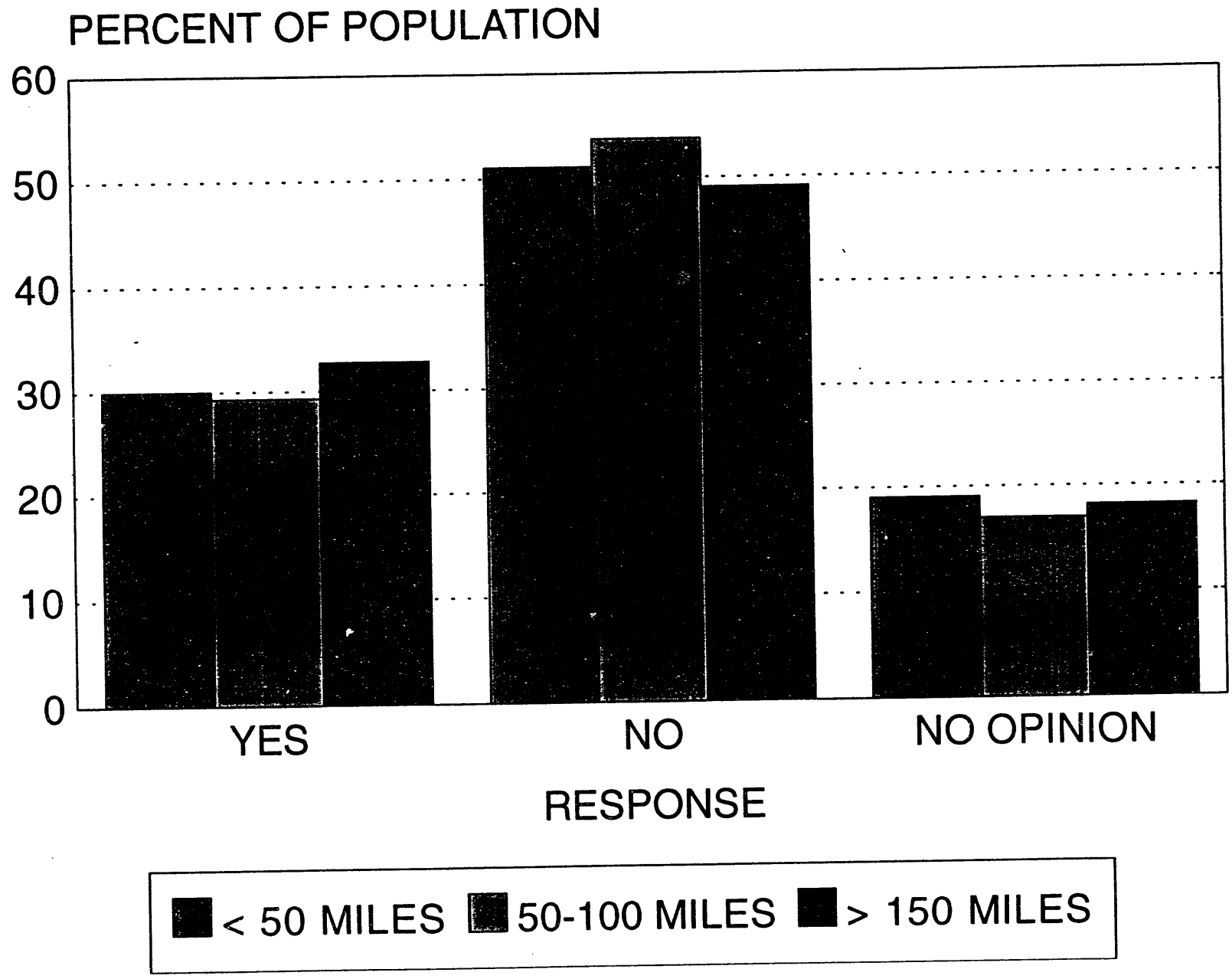
IF HARMFUL WATER POLLUTION, WHAT IS THE SOURCE



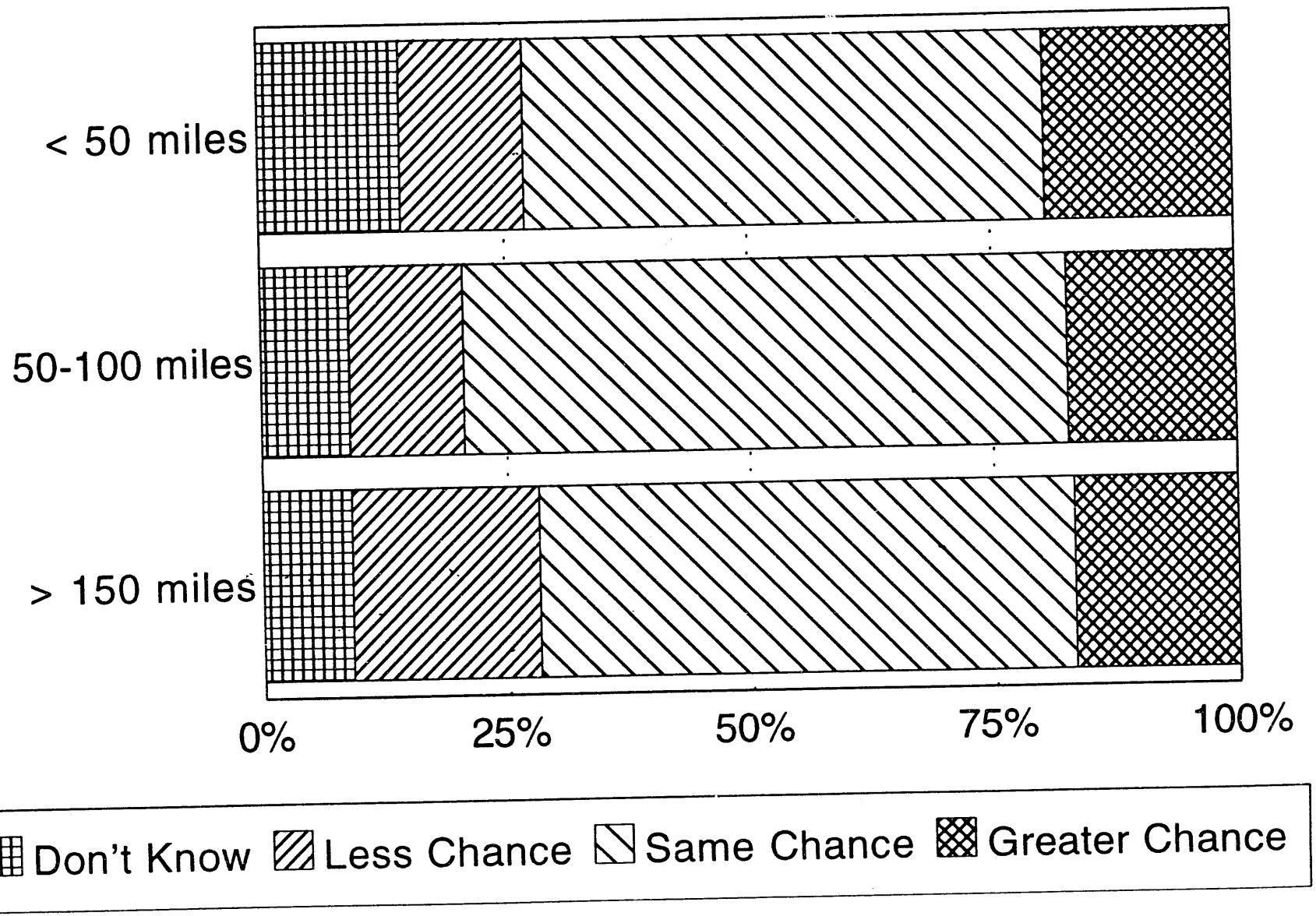
IF HARMFUL AIR POLLUTION, WHAT IS THE SOURCE



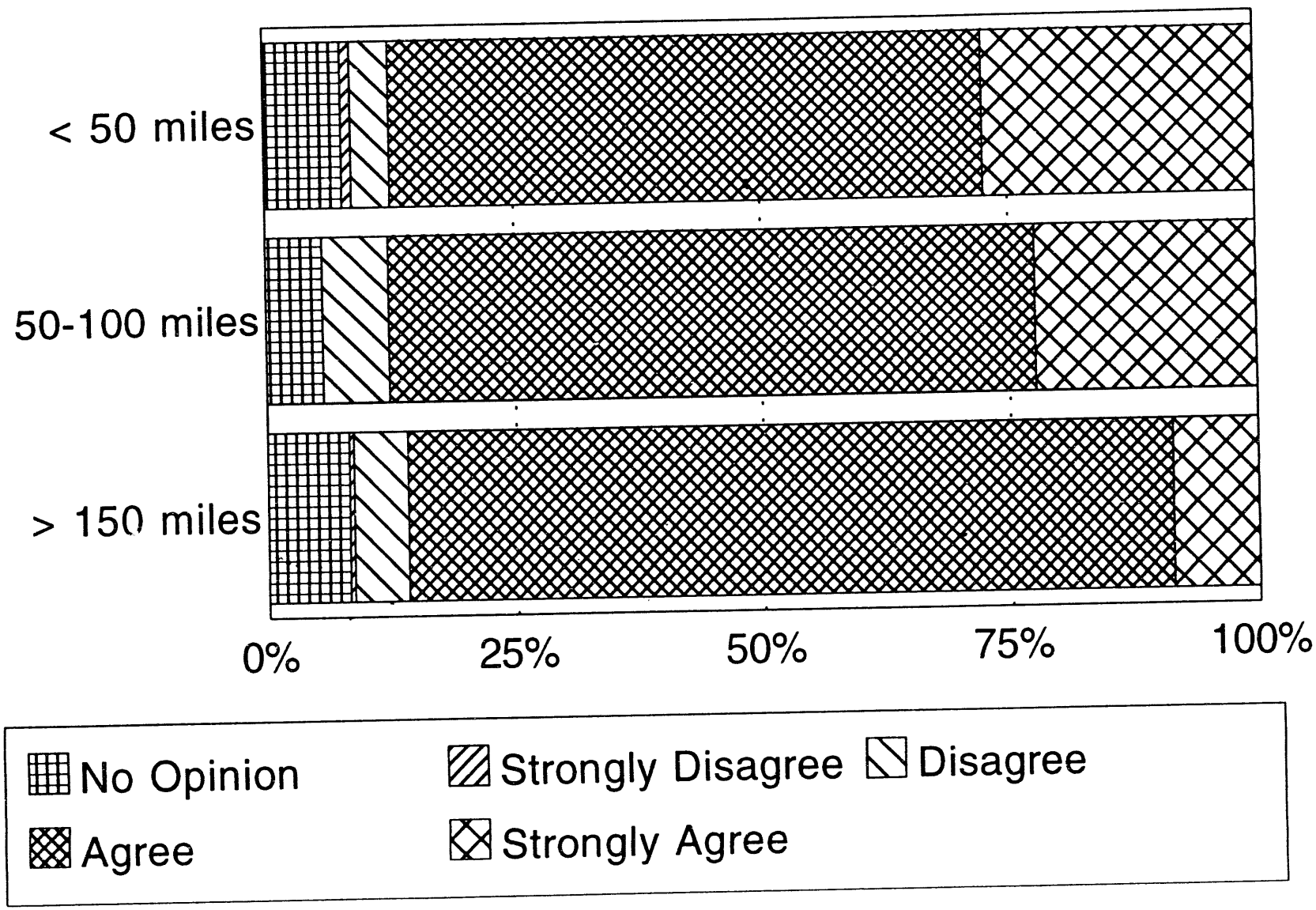
ARE THERE ENOUGH COMMUNITY POLLUTION STUDIES



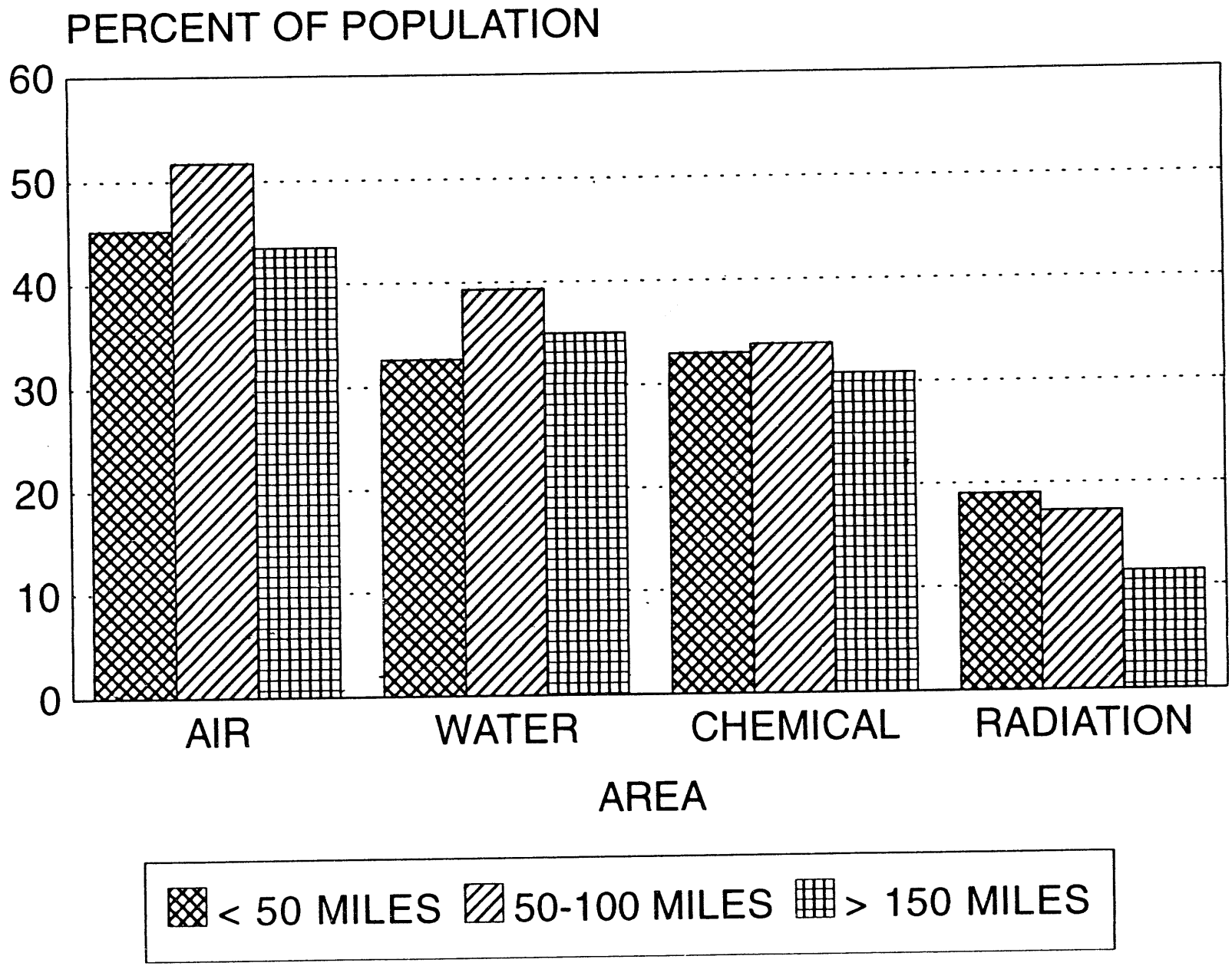
CHANCE OF GETTING CANCER COMPARED TO OTHERS IN THE STATE



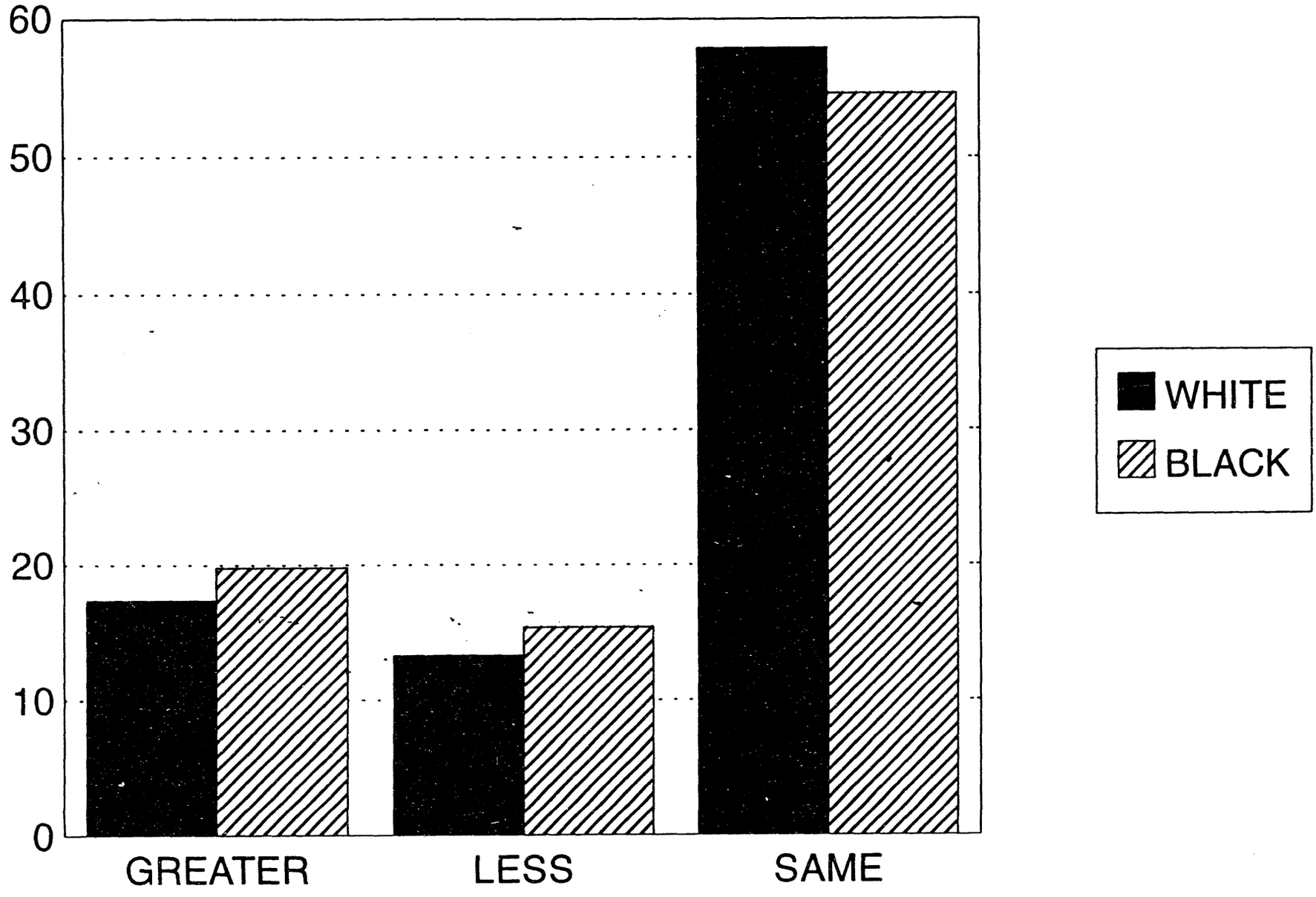
EXPOSED TO RADIATION, LIKELY TO SUFFER ADVERSE HEALTH EFFECTS



PUBLIC CONCERNS ABOUT POLLUTION PROBLEMS



CHANCE OF LOCAL COMMUNITY GETTING CANCER COMPARED TO STATE



4. (IF POLLUTION) What is the major pollution type?

Water	1	(Go to Question 6)
Air	2	(Go to Question 6)
Radiation	3	(Go to Question 6)
Other _____	6	(Go to Question 6)
Don't Know	7	(Go to Question 6)
Refused	9	(Go to Question 6)

5. (IF LESS CHANCE) Why do you think people in your community are less likely to get cancer?

No or Less Pollution	1
Genetics	2
Low Tobacco Products Use	3
Eating Habits	4
Occupation	5
Other _____	6
Don't Know	7
Refused	9

6. Considering the different types of cancer, what type of cancer do you think people in your community are most likely to get?

Lung	1
Breast	2
Prostate	3
Leukemia	4
Colon/Rectum	5
Other _____	6
Don't Know	7
Refused	9

7. My next question deals with heart disease and stroke, what do you feel is the major risk factor associated with these conditions?

Diet 1

High Blood Pressure 2

Lack of Exercise 3

High Cholesterol 4

Cigarette Smoking 5

Stress 6

Other 8

Don't Know 7

Refused 9

8. Do you feel there is any air pollution in your community that could be harmful to your health?

Yes 1

No ..... 2 (Go to Question 9)

Don't Know ..... 7 (Go to Question 9)

Refused ..... 9 (Go to Question 9)

9. (IF YES) Where do you think the air pollution comes from?

Cars/Exhaust 1

Industry 2

Savannah River Site 3

Other _____ 6

Don't Know 7

Refused 9

10. Do you feel there is any drinking water pollution in your community that could be harmful to your health?

Yes 1

No ..... 2 (Go to Question 11)

Don't Know ..... 7 (Go to Question 11)

Refused ..... 9 (Go to Question 11)

11. (IF YES) Where do you think the water pollution comes from?

Industry 1

Waste Site/Dump..... 2

Pesticide/Farms 3

Savannah River Site 4

Other _____ 6

Don't Know 7

Refused 9

12. Do you feel there is any chemical pollution in your community that could be harmful to health?

Yes..... 1

No..... 2

Don't Know 7

Refused 9

13. Do you feel there is any radiation pollution in your community that could be harmful to health?

Yes..... 1

No..... 2

Don't Know 7

Refused 9

14. From which of the following sources do you get information regarding pollution in your community?

	Yes	No
Newspapers	1	2
Television	1	2
Radio	1	2
Physician	1	2
Health Department	1	2
Industry Officials	1	2

15. Of these sources, which one do you feel provides the most accurate information?

Newspapers 1

Television 2

Radio..... 3

Physician..... 4

Health Department..... 5

Industry Officials 6

Don't Know 7

Refused..... 9

16. Do you feel enough study of pollution is being done in your community?

Yes..... 1 (Go to Question 17)

No..... 2

Don't Know ..... 7 (Go to Question 17)

Refused ..... 9 (Go to Question 17)

17. (IF NO) What agency or group do you feel should do the studies of pollution?

State/Local Health Department . 1

University 2

Federal Government 3

Other _____ . 6

Don't Know..... 7

Refused 9

18. Dose - Use Relationships

	Strongly Disagree	Disagree	Agree	Strongly Agree	No Opinion
A. If you are exposed to a toxic chemical substance, then you are likely to suffer adverse health effects.	1	2	3	4	5
B. If you are exposed to radiation, then you are likely to suffer adverse health effects.	1	2	3	4	5

19. Animal Studies

A. The way that an animal reacts to a chemical is a reliable predictor of how a human would react to the same chemical.	1	2	3	4	5

20. Attitudes

A. The land, air and water around us are, in general, more contaminated now than ever before.	1	2	3	4	5
B. Use of chemicals has improved our health more than it has harmed.	1	2	3	4	5
C. Use of radiation has improved our health more than it has harmed.	1	2	3	4	5
D. People worry unnecessarily about what chemicals can do to their health.	1	2	3	4	5
E. Chemicals are a major force behind technological advancement.	1	2	3	4	5
F. Radiation is a major force behind technological advancement.	1	2	3	4	5

21. Risk Reduction Attitudes

A. It can never be too expensive to reduce the risks associated with chemicals.	1	2	3	4	5
B. There is always a risk when using chemicals.	1	2	3	4	5
C. I think that I should know as much as I can about the chemicals around me.	1	2	3	4	5

22. Have you ever heard of the Savannah River Region Health Information System?

Yes. 1

No. . . . . 2 (Go to Question 23)

Don't Know . . . . . 7 (Go to Question 23)

Refused . . . . . 9 (Go to Question 23)

23. (IF YES) Where is the System located?

MUSC..... 1

Other _____ 6

Don't Know 7

Refused 9

24. Have you ever heard of the Environmental Hazards Assessment Program?

Yes..... 1

No..... 2 (Go to Question 25)

Don't Know ..... 7 (Go to Question 25)

Refused ..... 9 (Go to Question 25)

25. (IF YES) Where is the program located?

MUSC..... 1

Other _____ 6

Don't Know 7

Refused..... 9

ACTIONS

26. Please answer the following questions concerning any of the things that you have done to express your views or concerns that apply to pollution.

	Yes	No	Don't Know	Refused
A. Written a letter to a public official.	1	2	7	9
B. Voted for or against a candidate for public office in part because of his or her position on this issue.	1	2	7	9
C. Attended a public hearing or meeting concerning this issue.	1	2	7	9
D. Joined or contributed money to a special interest group or organization	1	2	7	9
E. Boycotted a company.	1	2	7	9
F. Contacted a physician about health concerns regarding this issue.	1	2	7	9
G. Altered or changed your lifestyle or health practices.	1	2	7	9

27. Overall, do you feel the Savannah River Site is good for the state or bad for the state?

Good..... 1

Bad..... 2

Neutral 3

Don't Know 7

Refused..... 9

PART VI: DEMOGRAPHICS

And, finally, these next few questions ask for a little more information about you.

28. How old were you on your last birthday?

a. CODE AGE IN YEARS ..... ____ ____

Don't know/not sure 0 7

Refused 0 9

29. What is your race?

Would you say:

(PLEASE READ)

a. White 1

b. Black 2

c. Other - specify . . . (_____)..... 6

Don't know/not sure 7

Refused 9

30. What is the highest grade or year of school you completed?

(READ ONLY IF NECESSARY)

a. Eighth Grade or Less 1

b. Some High School 2

c. High School Grad or GED Certificate 3

d. Some Technical School 4

e. Technical School Graduate 5

f. Some College 6

g. College Graduate 7

h. Post Grad or Professional Degree 8

Refused 9

31. Are you currently: (PLEASE READ)

a. Employed for wages 1

b. Self employed 2

c. Out of work for more than 1 year 3

d. Out of work for less than 1 year 4

e. Homemaker 5

f. Student 6

g. Retired 7

Refused 9

32. And are you: (PLEASE READ)

a. Married 1

b. Divorced 2

c. Widowed 3

d. Separated 4

e. Never been married 5

f. A member of an unmarried couple 6

Refused 9

33. Which of the following categories best describes your annual household income from all sources? (PLEASE READ)

a. Less than 10,000 1

b. 10 to 15,000 2

c. 15 to 20,000 3

d. 20 to 25,000 4

e. 25 to 35,000 5

f. 35 to 50,000 6

g. Over 50,000 8

Don't know/Not sure 7

Refused 9

34. How many years altogether have you lived in this state?

a. CODE YEARS. ..... ___

Don't know/Not sure 7 7

Refused 9 9

35. Are you a current cigarette smoker?

Yes 1

No 2

Refused 9

36. Have you been told you have high blood pressure?

Yes 1

No ..... 2 (Skip to Q 38)

Don't Know ..... 7 (Skip to Q 38)

Refused ..... 9 (Skip to Q 38)

37. Are you taking medication for high blood pressure?

Yes 1

No 2

Don't Know 7

Refused 9

38. INTERVIEWER: INDICATE SEX OF RESPONDENT ASK IF NECESSARY

a. Male 1

b. Female 2

39. How many telephone numbers will reach this household, including the number I used today?

DIFFERENTIATE BETWEEN TELEPHONE NUMBERS AND TELEPHONE SETS IF NECESSARY. INCLUDE ALL TELEPHONE NUMBERS THAT CAN REACH HOUSEHOLD

A. Total Telephone Numbers ..... ____

CLOSING STATEMENT

That's my last question. Everyone's answers will be combined to give us information about the opinions of the people in this community. Thank you very much for your time and cooperation. You will be contacted in the near future about participation in the next phase of the study.

METHODS

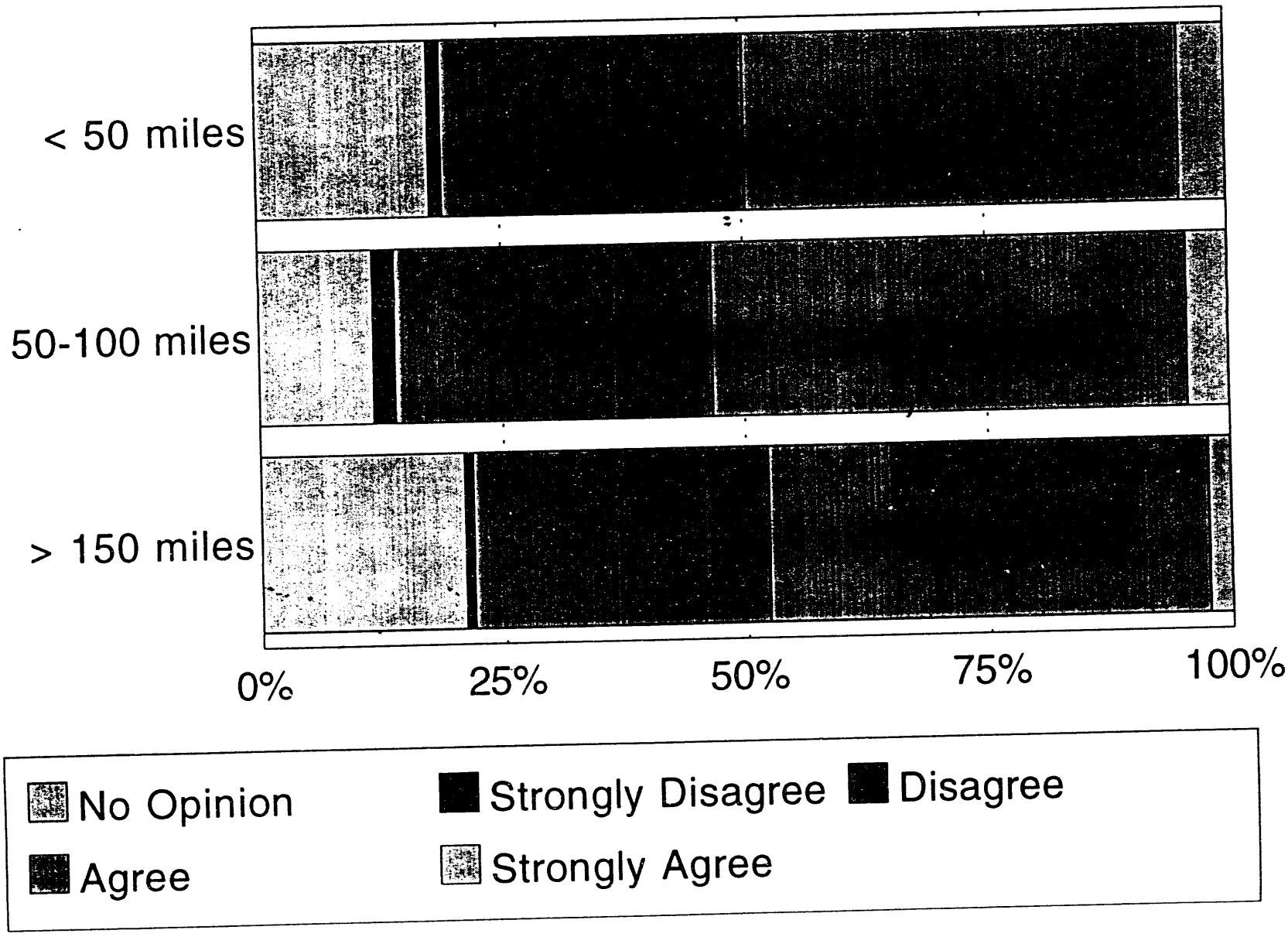
- STUDY AREAS
  THREE GEOGRAPHIC AREAS AROUND THE SAVANNAH RIVER SITE WERE SELECTED. THESE AREAS HAD EQUAL DEMOGRAPHIC CHARACTERISTICS.

- ASSESSMENT
  A SAMPLE WAS SELECTED AND ASSESSED USING A RANDOM DIGIT-DIALING TELEPHONE SURVEY METHODOLOGY.

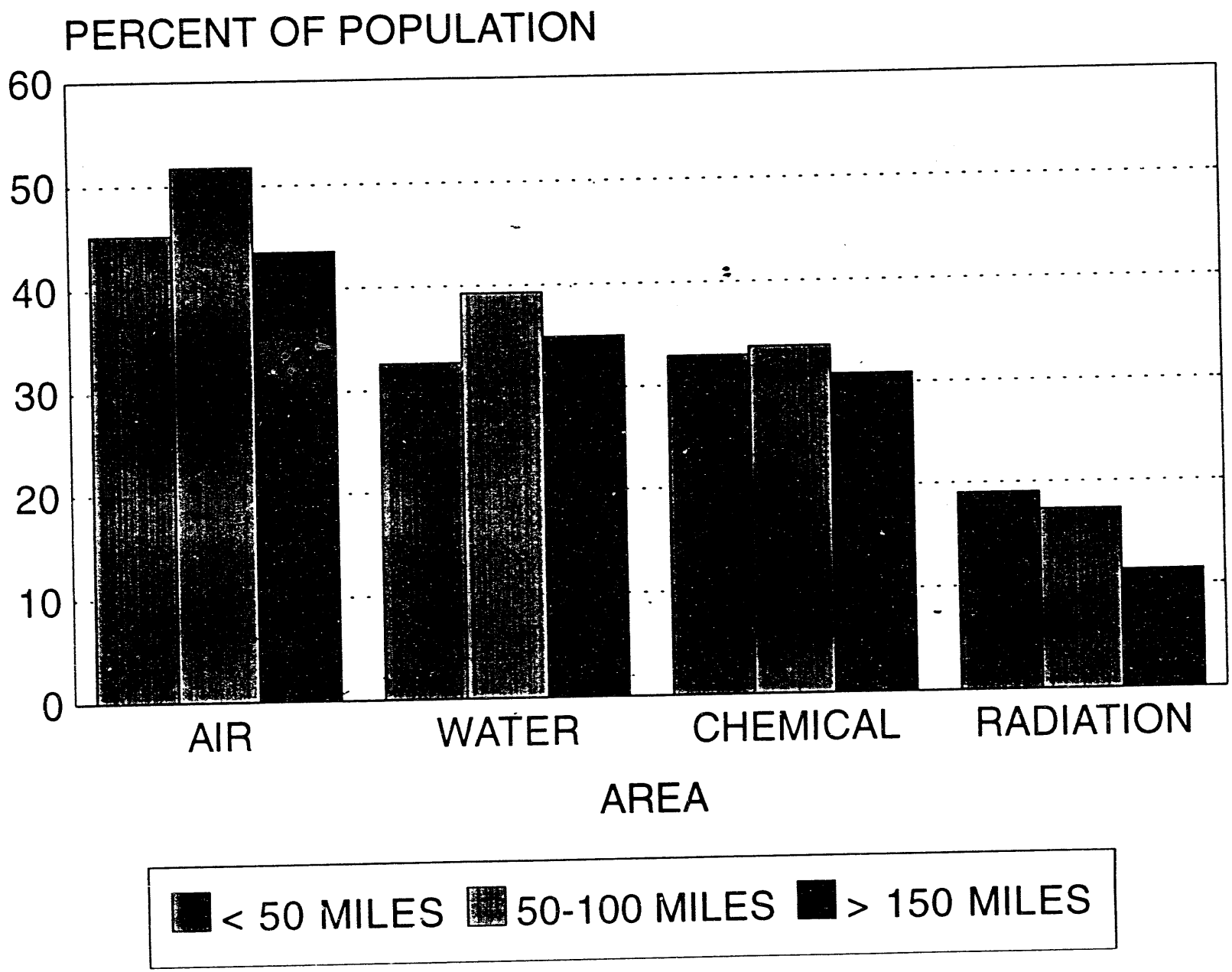
FIRST IMAGE WHEN RESPONDENT HEARS "SAVANNAH RIVER SITE"

	< 50 MILES	50-100 MILES	> 150 MILES
DANGER	3.4%	3.0%	2.3%
HEALTH CONCERNS	2.8%	2.6%	0.5%
NEGATIVE IMAGE	0.9%	1.0%	0.9%
POLLUTION/HARMFUL TO ENVIRONMENT	9.9%	20.7%	5.1%
WAR/BOMBS	5.6%	1.6%	0.0%
RADIATION/CHEMICALS	15.5%	16.7%	11.1%
UNNECESSARY	0.9%	0.7%	1.4%
NUCLEAR/ATOMIC ENERGY	7.1%	5.2%	2.3%
NEGATIVE ECONOMIC	1.5%	0.3%	0.0%
NUCLEAR/CHEMICAL WASTES	2.8%	4.6%	2.3%
INCORRECT OR VAGUE LOCATIONS	1.2%	1.0%	6.0%
CORRECT LOCATION	0.6%	0.7%	0.0%
PLANT/FACILITY/SIZE	5.3%	0.3%	0.0%
GOVERNMENT/INDUSTRY/BUSINESS/OWNER	2.8%	1.0%	1.4%
EMPLOYMENT/POSITIVE ECONOMIC	20.4%	2.0%	3.7%
SECURITY/SAFETY REGULATIONS	0.9%	0.3%	0.0%
NO IMAGE	13.9%	19.7%	15.7%
NEVER HEARD OF SRS	0.9%	9.5%	38.9%
OTHER	0.0%	0.7%	0.0%

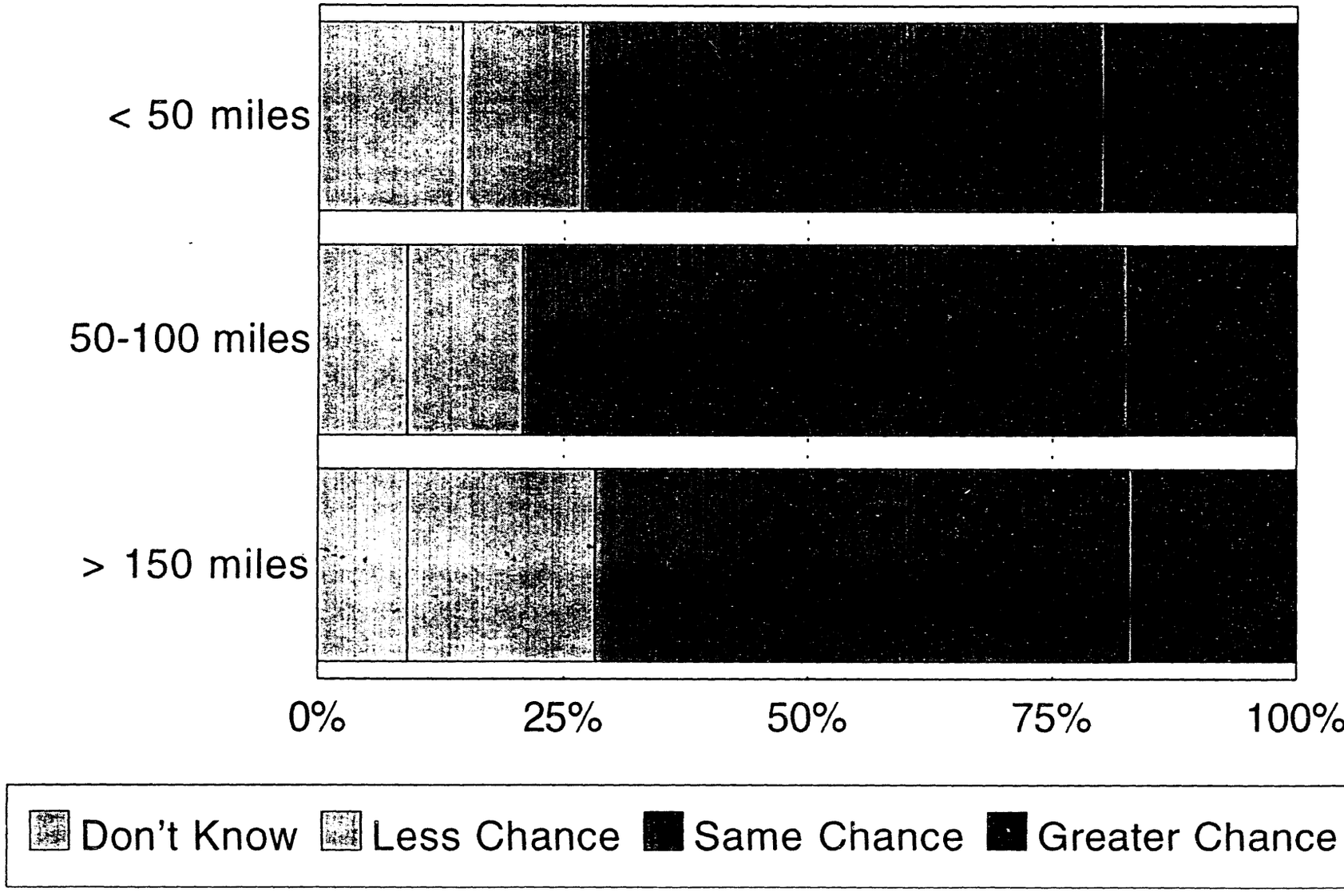
WAY ANIMAL REACTS TO CHEMICALS IS A RELIABLE PREDICTOR OF HUMAN REACTION



PUBLIC CONCERNS ABOUT POLLUTION PROBLEMS



CHANCE OF GETTING CANCER COMPARED TO OTHERS IN THE STATE



REASONS FOR GREATER CANCER RISK

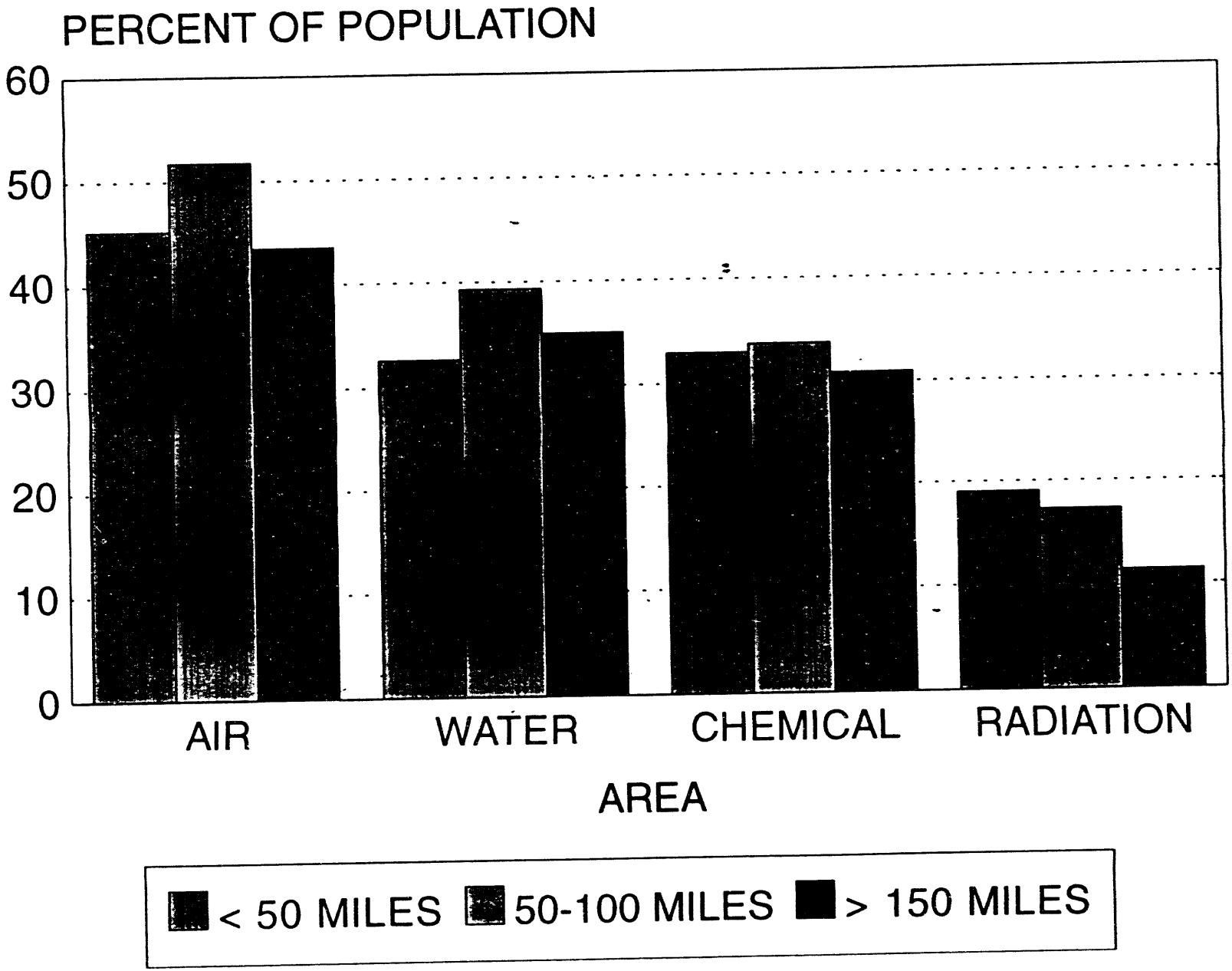
	< 50 MILES	50-100 MILES	> 150 MILES
POLLUTION	55.7%	67.3%	43.2%
GENETICS	3.3%	3.8%	8.1%
TOBACCO	8.2%	9.6%	18.9%
NUTRITION	4.9%	3.8%	13.5%
OCCUPATION	6.6%	3.8%	0.0%

TYPE OF CANCER MOST COMMON IN AREA

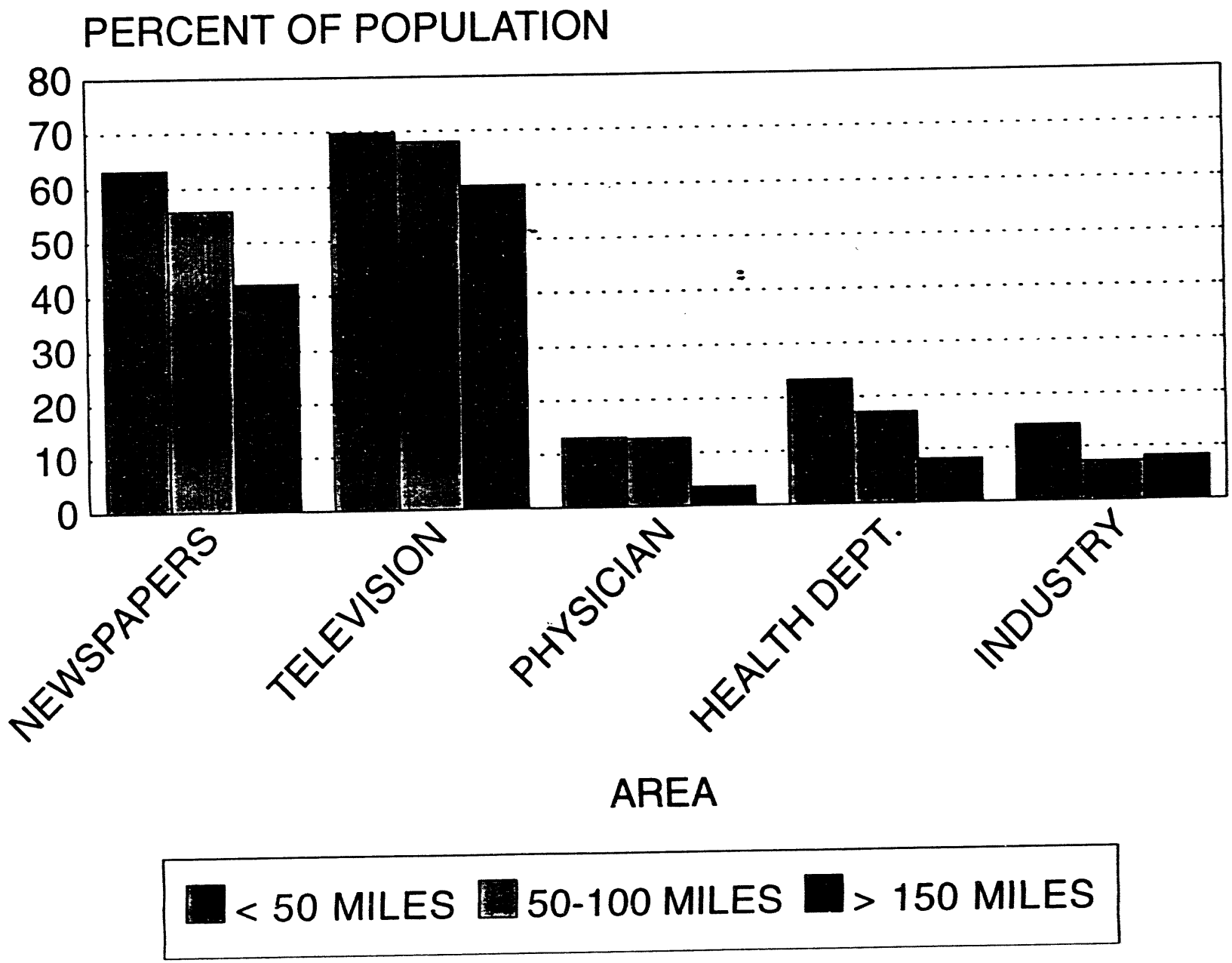
PUBLIC PERCEPTION

	< 50 MILES	50-100 MILES	> 150 MILES
LUNG	45.5%	42.0%	49.5%
BREAST	11.0%	15.7%	13.2%
PROSTATE	3.5%	4.3%	5.9%
LEUKEMIA	2.9%	3.7%	4.5%
COLON/RECTUM	7.7%	5.7%	7.3%
OTHER	29.4%	28.6%	19.6%

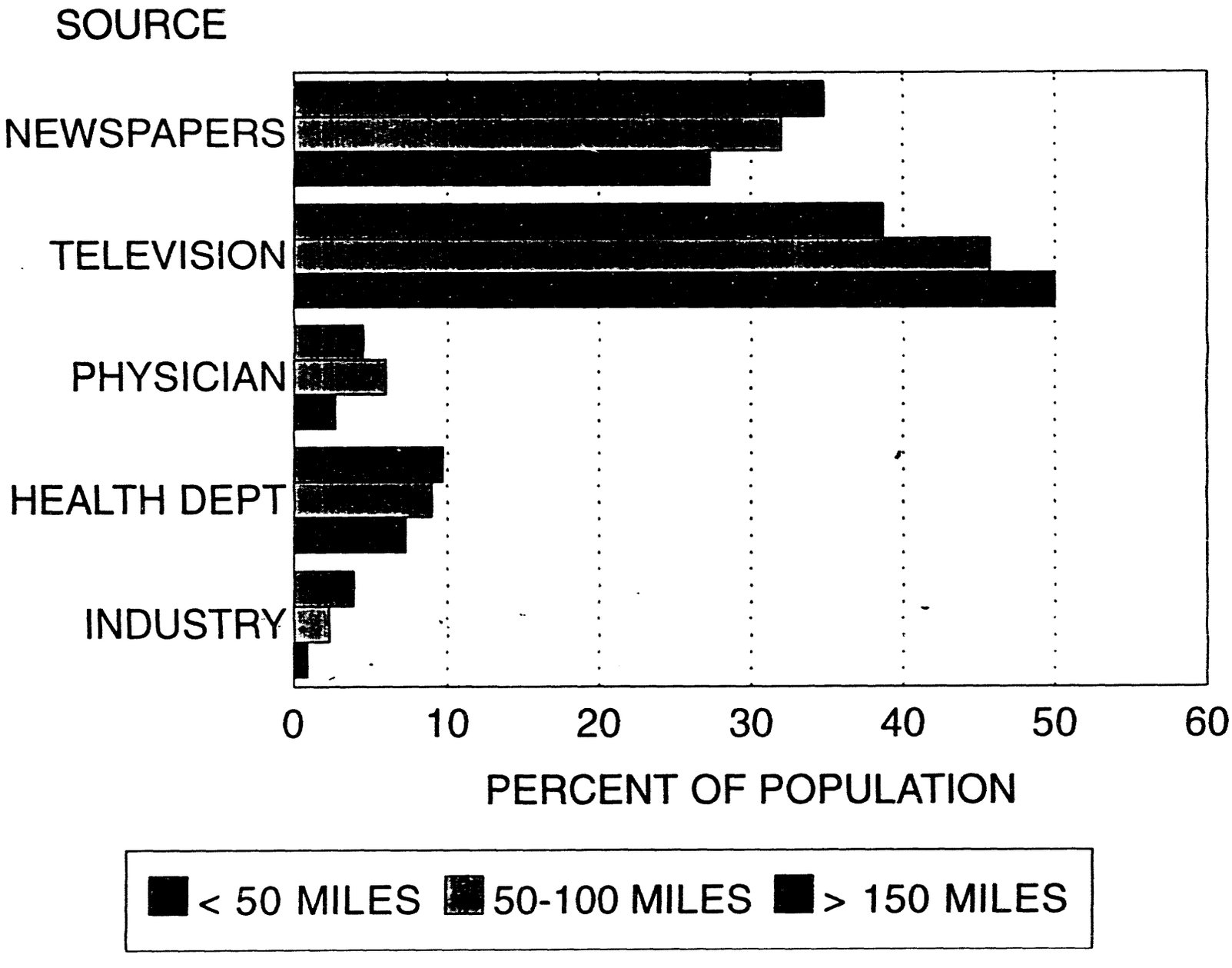
PUBLIC CONCERNS ABOUT POLLUTION PROBLEMS



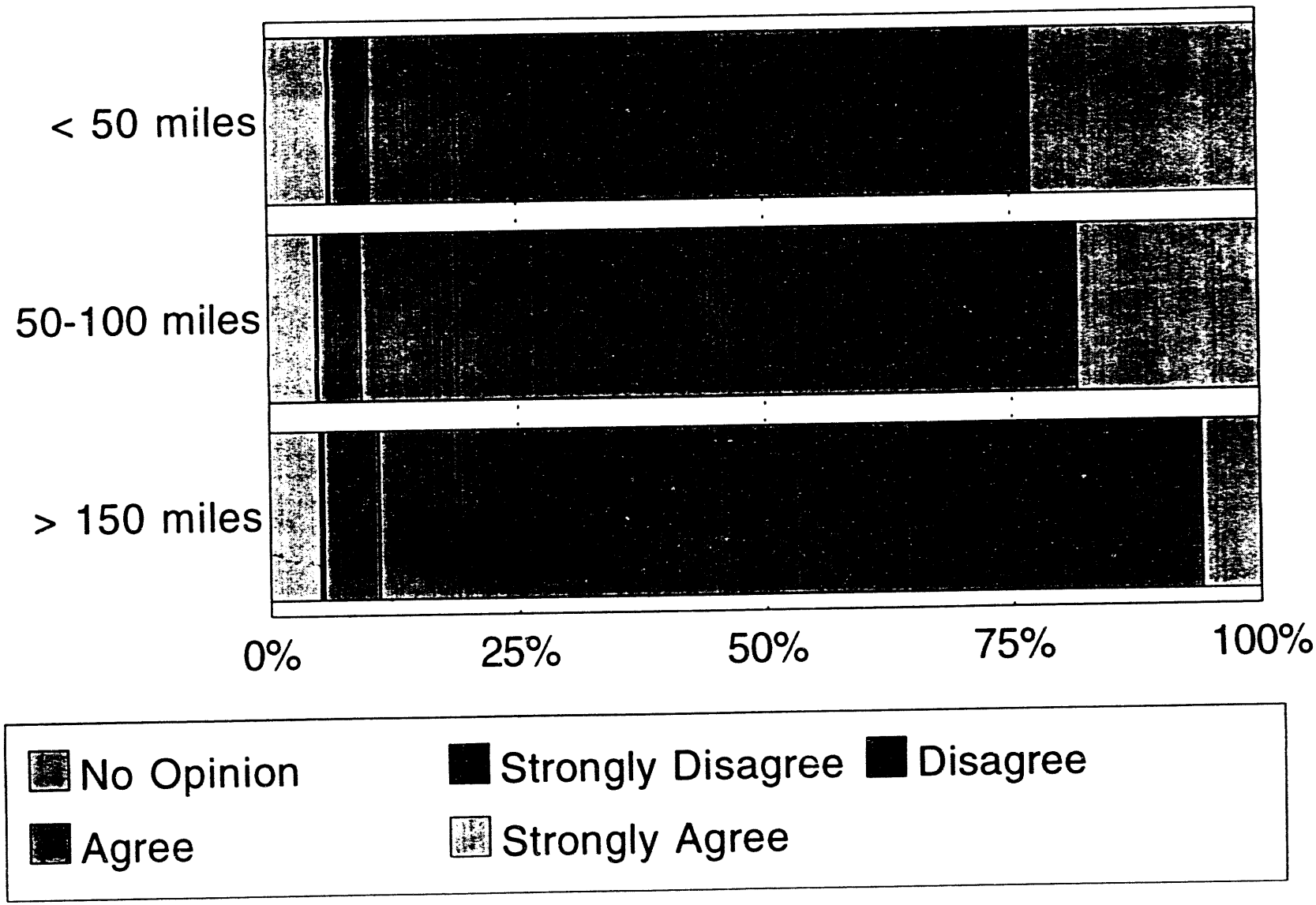
INFORMATION SOURCES FOR POLLUTION AND HEALTH



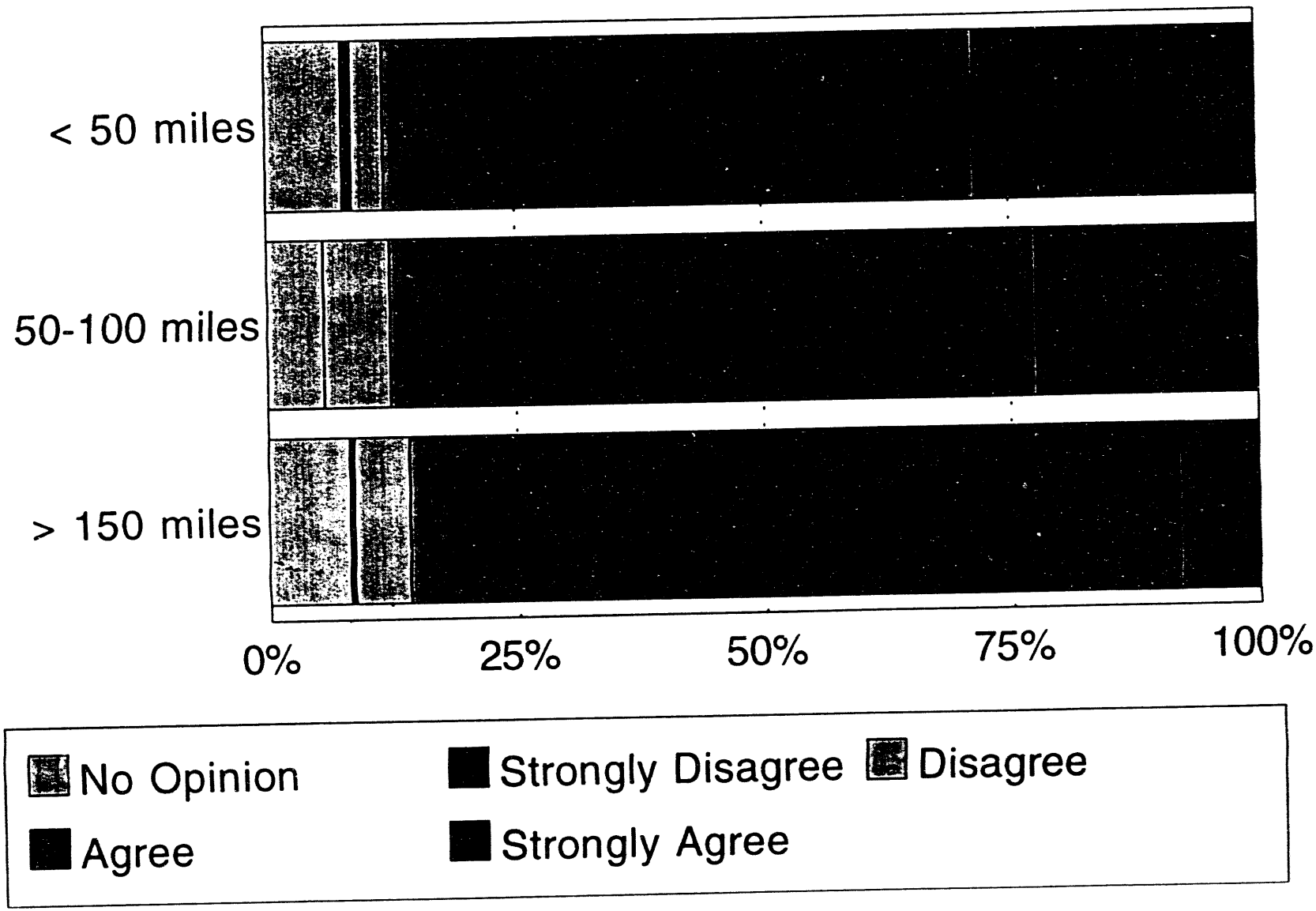
SOURCE WITH MOST ACCURATE INFORMATION



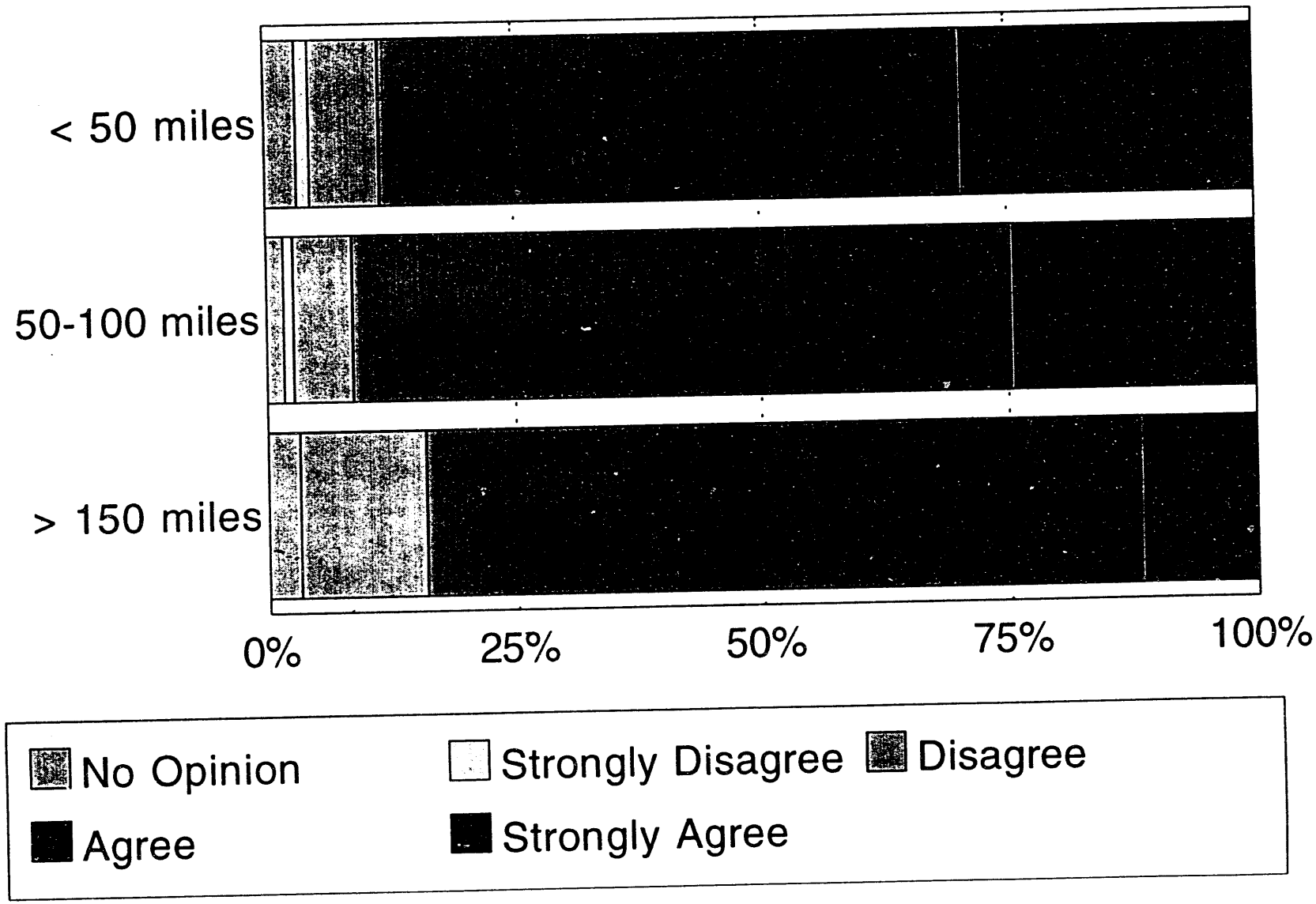
EXPOSED TO A TOXIC CHEMICAL, LIKELY TO SUFFER ADVERSE HEALTH EFFECTS



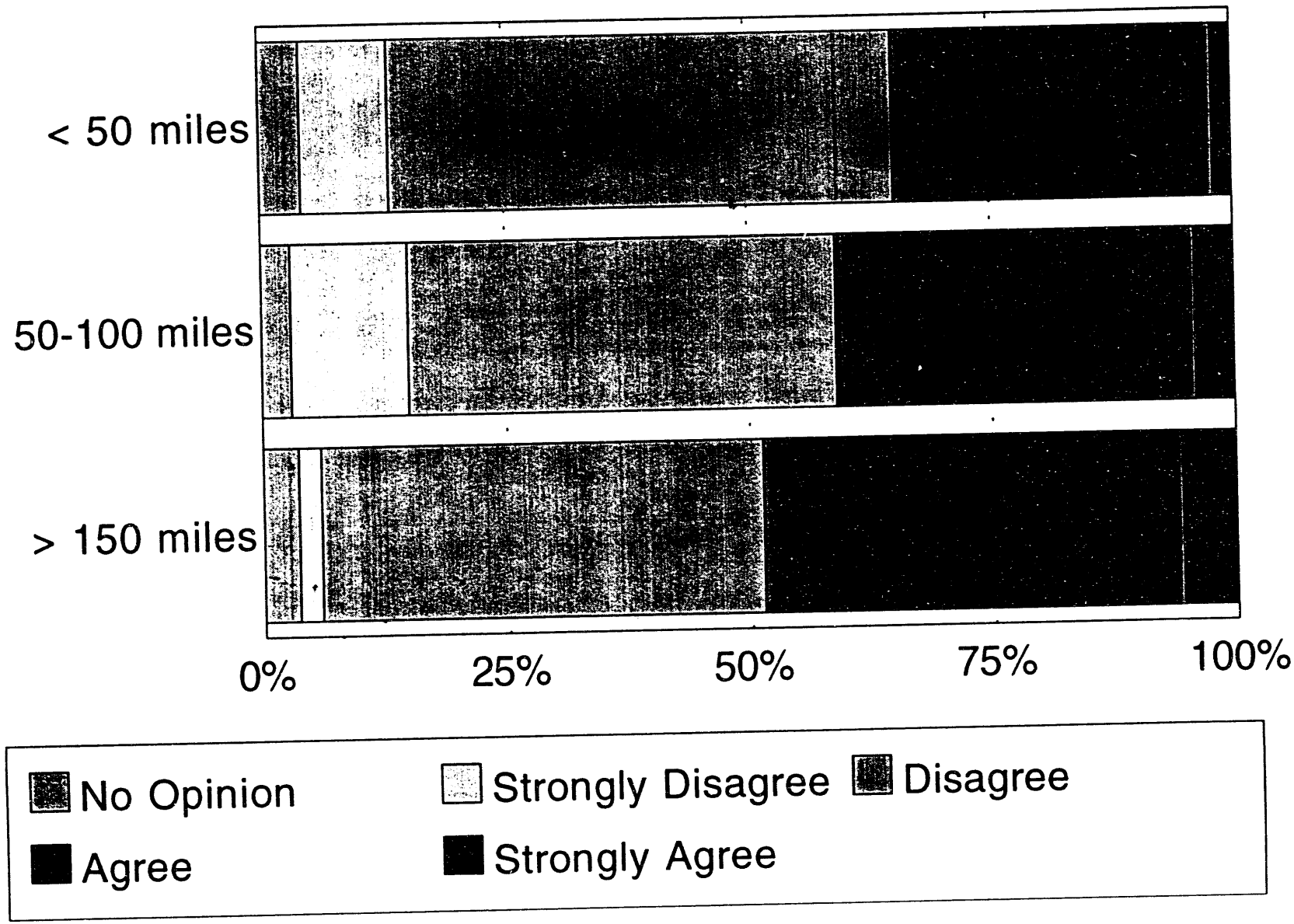
EXPOSED TO RADIATION, LIKELY TO SUFFER ADVERSE HEALTH EFFECTS



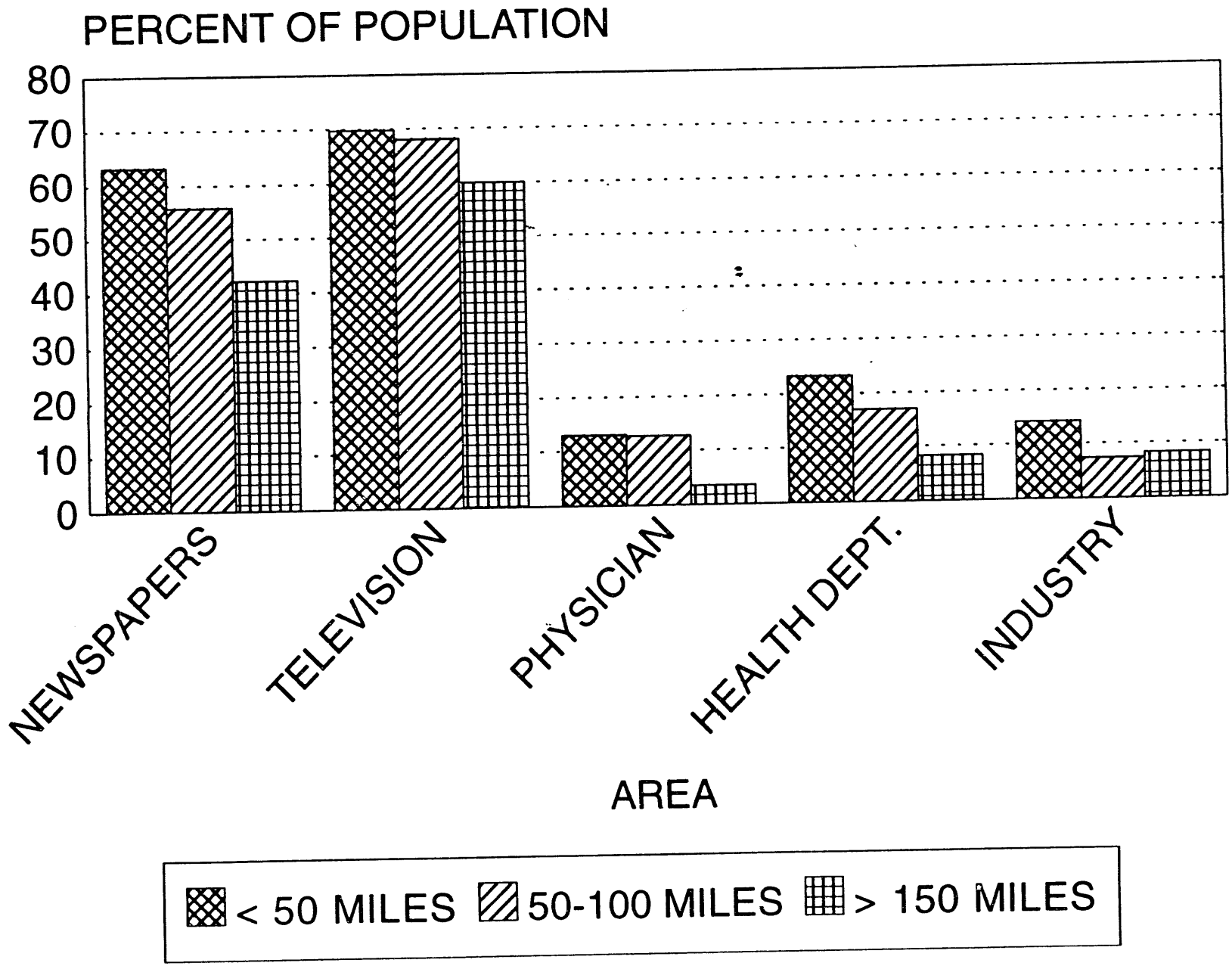
LAND, AIR AND WATER ARE MORE CONTAMINATED TODAY THAN EVER



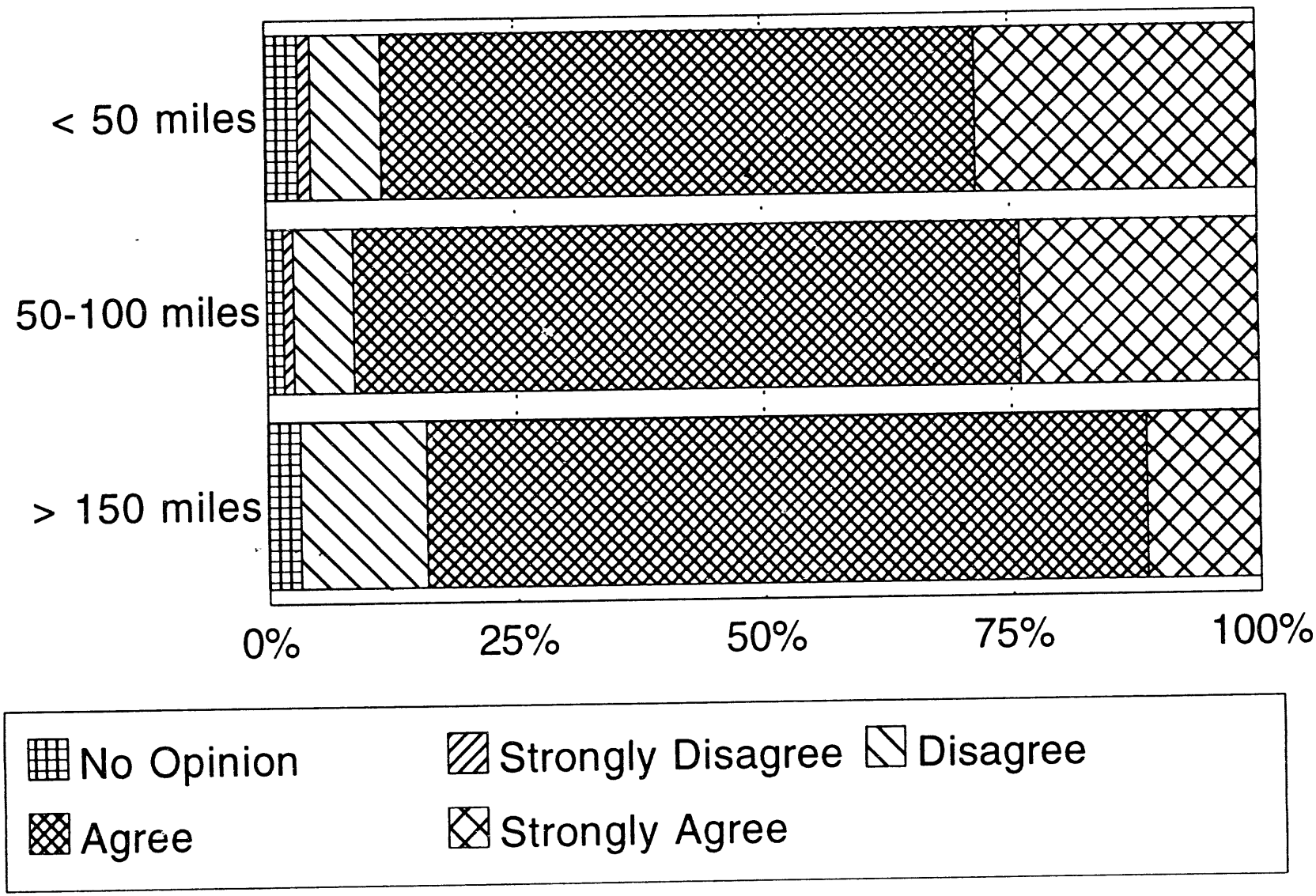
PEOPLE WORRY UNNECESSARILY ABOUT WHAT CHEMICALS CAN DO TO THEIR HEALTH



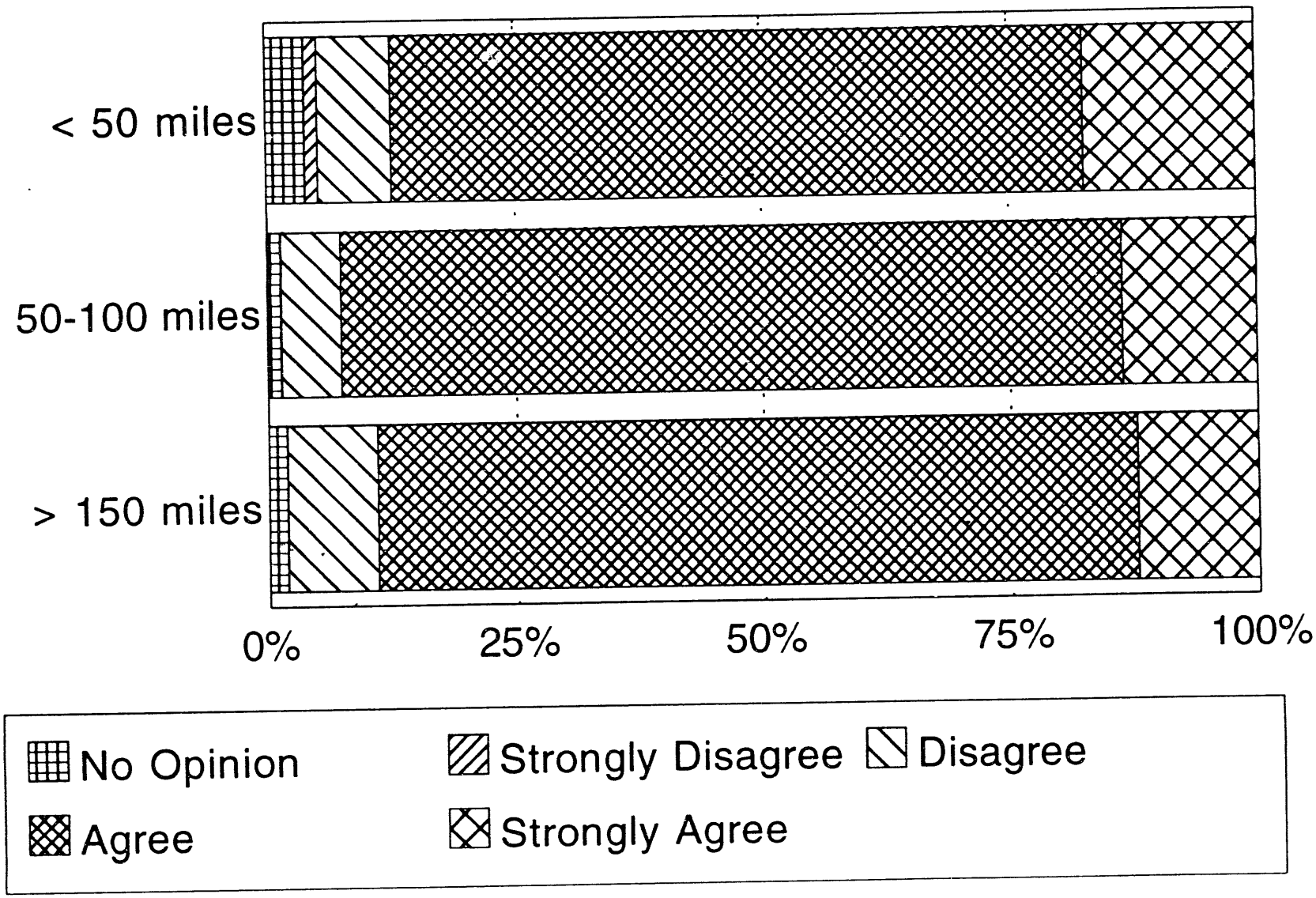
INFORMATION SOURCES FOR POLLUTION AND HEALTH



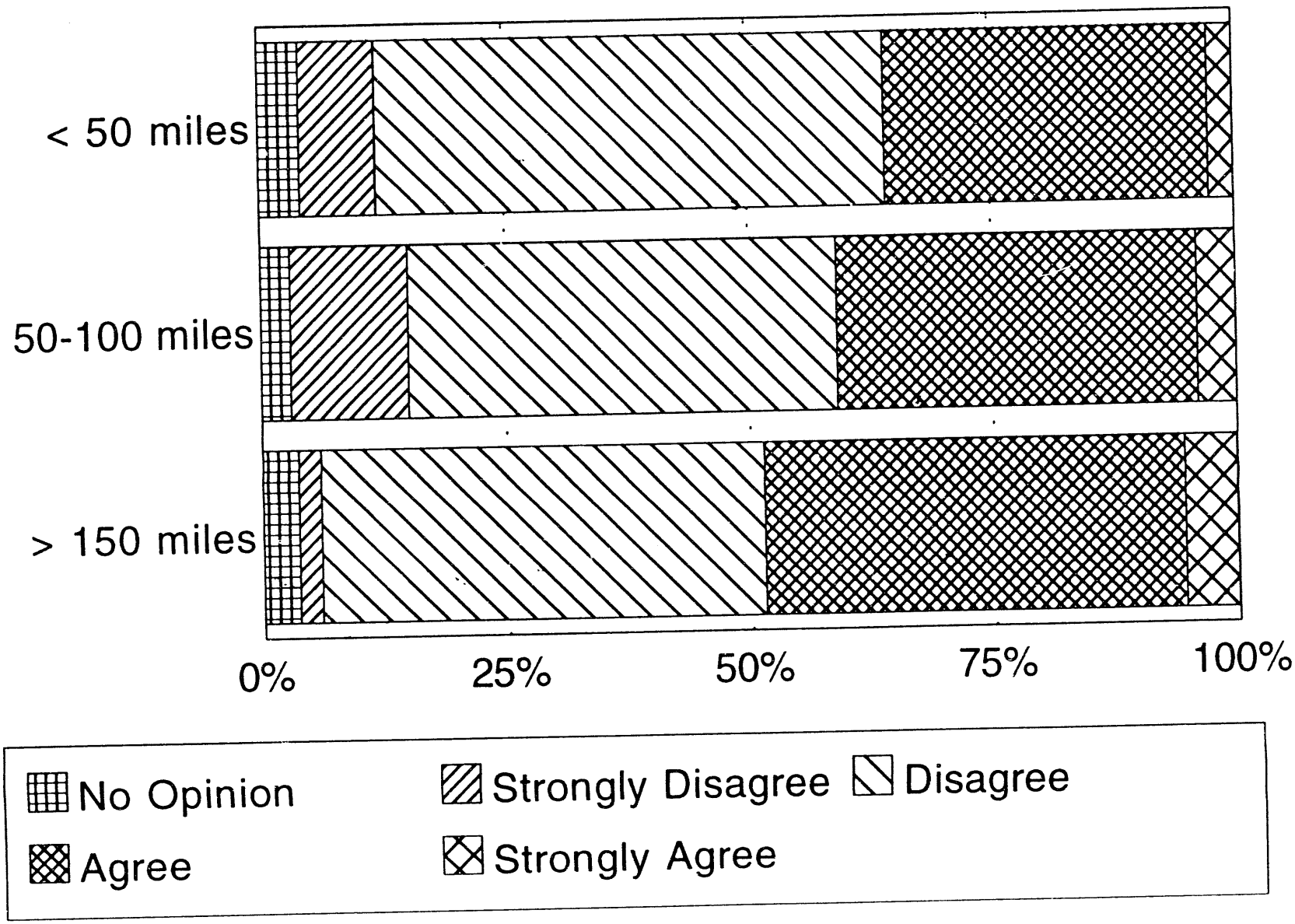
LAND, AIR AND WATER ARE MORE CONTAMINATED TODAY THAN EVER



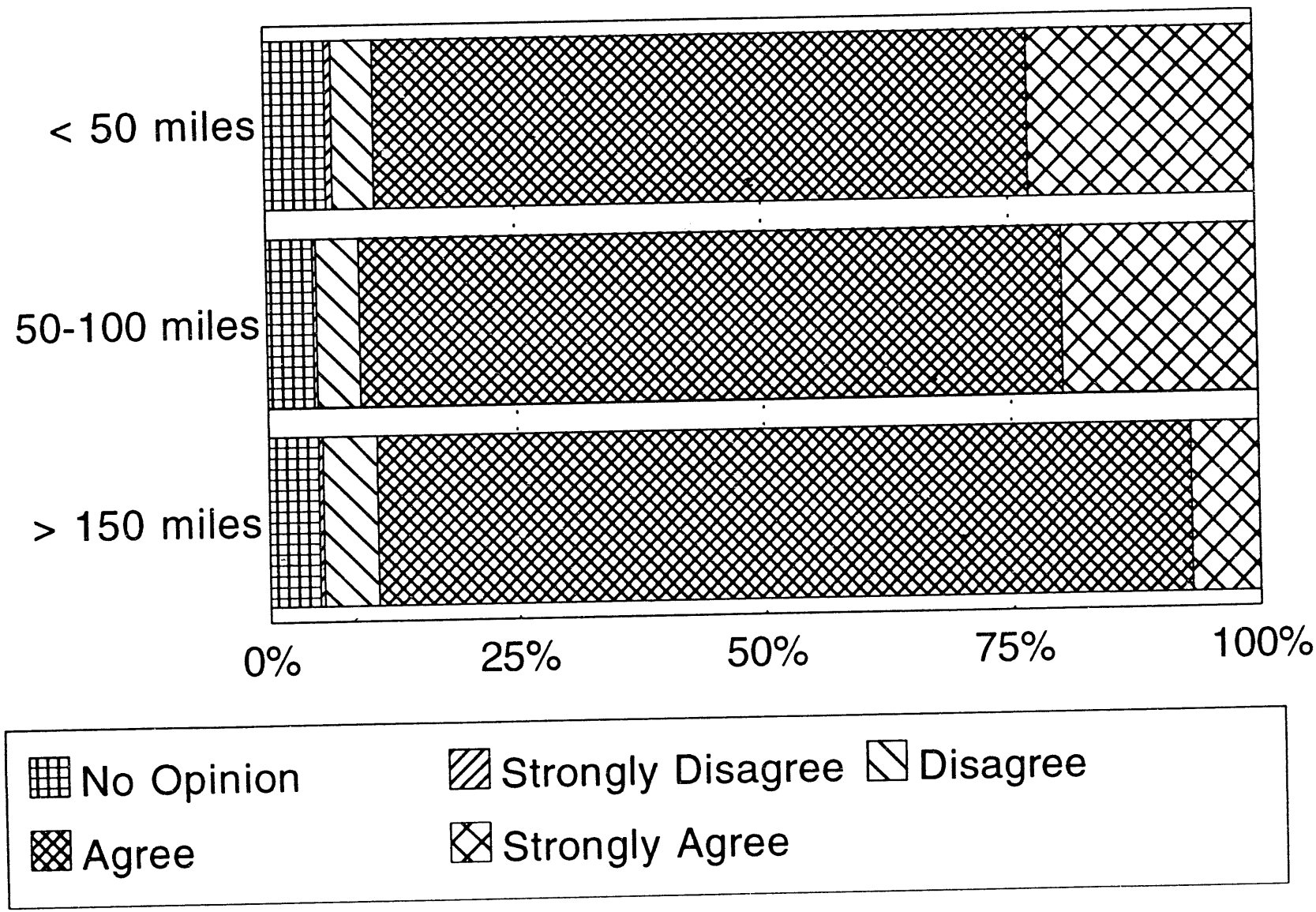
THERE IS ALWAYS A RISK WHEN USING CHEMICALS



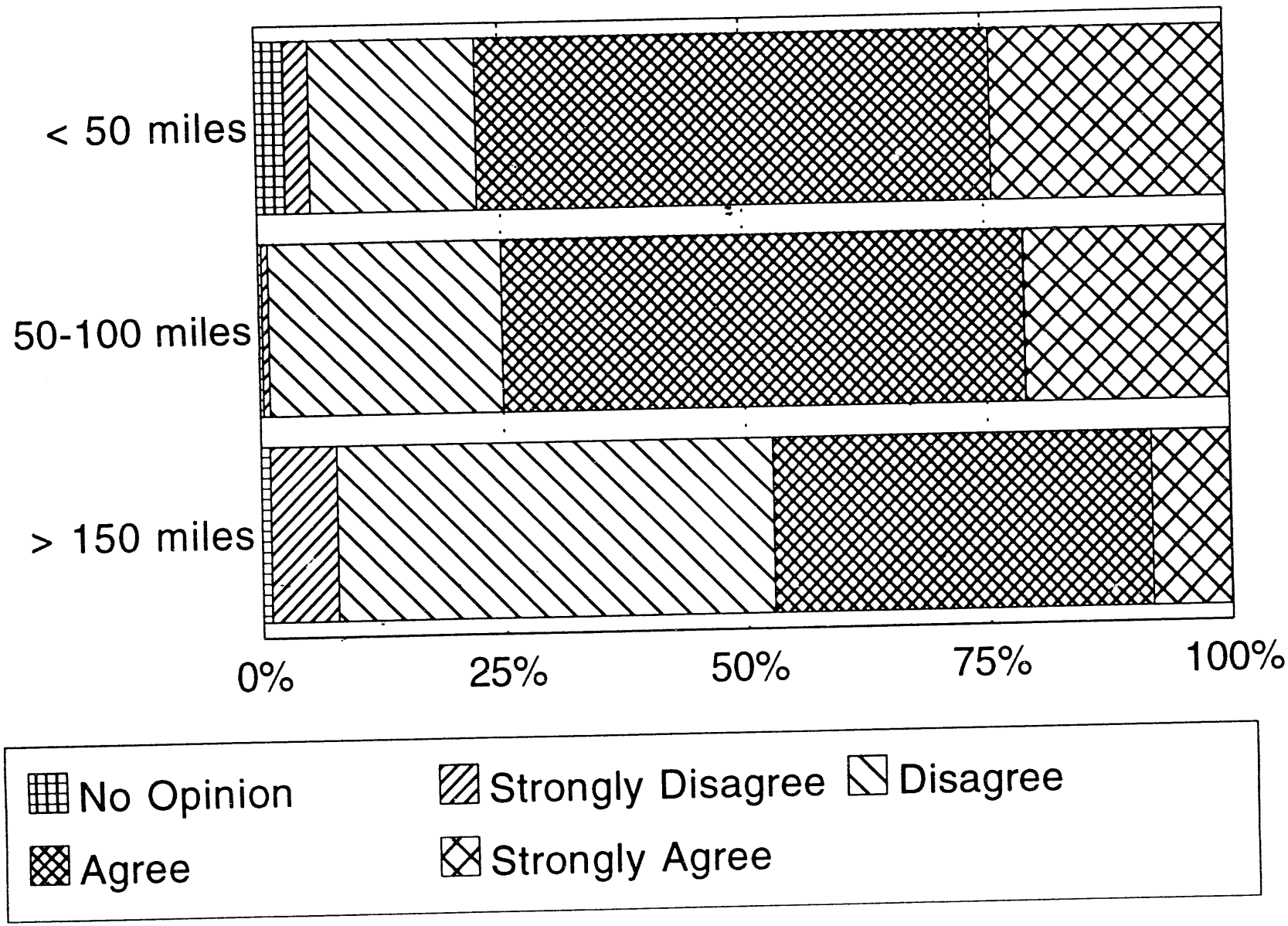
PEOPLE WORRY UNNECESSARILY ABOUT WHAT CHEMICALS CAN DO TO THEIR HEALTH



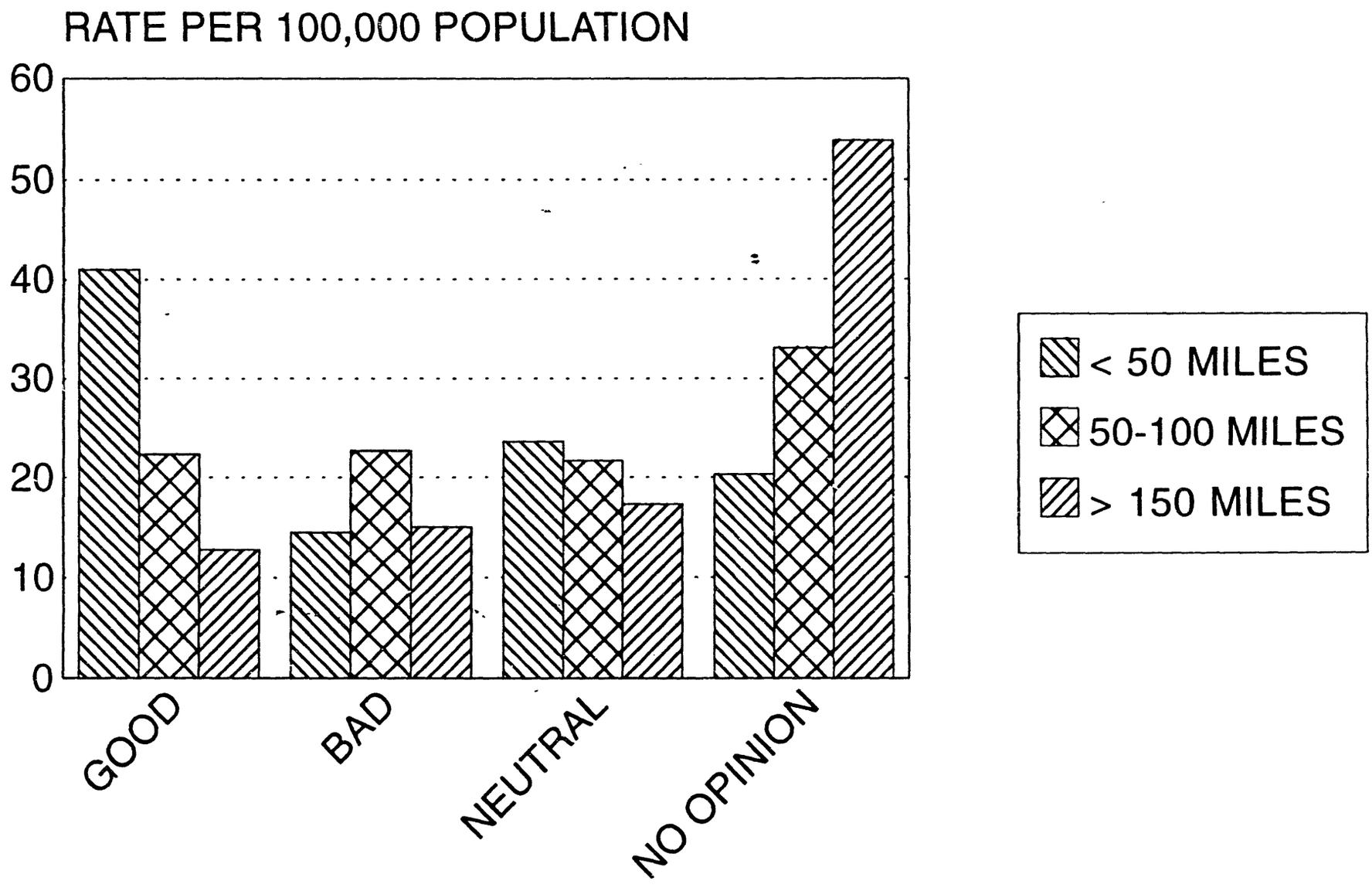
EXPOSED TO A TOXIC CHEMICAL, LIKELY TO SUFFER ADVERSE HEALTH EFFECTS



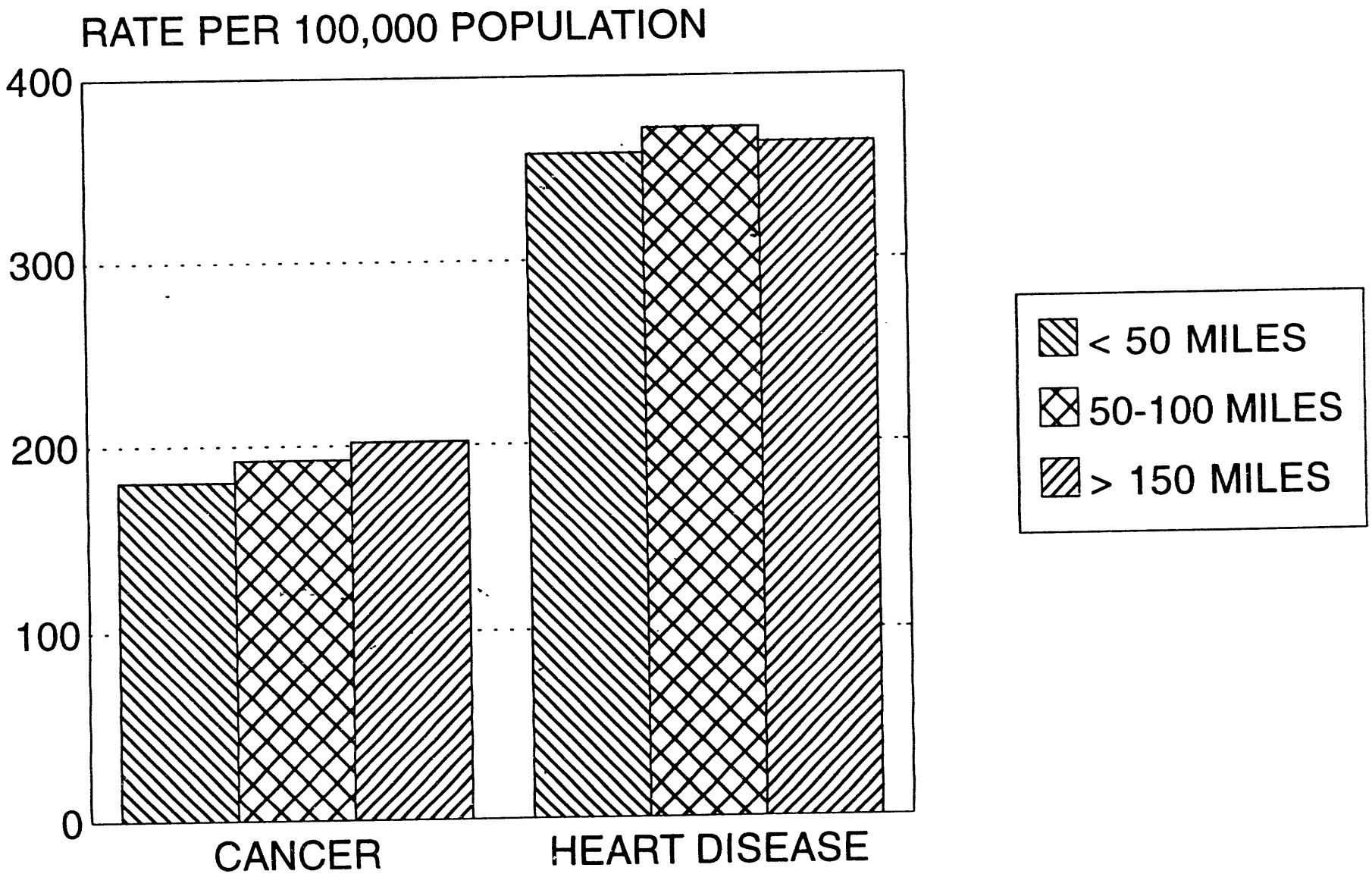
SHOULD KNOW AS MUCH AS POSSIBLE ABOUT THE CHEMICALS IN THE ENVIRONMENT



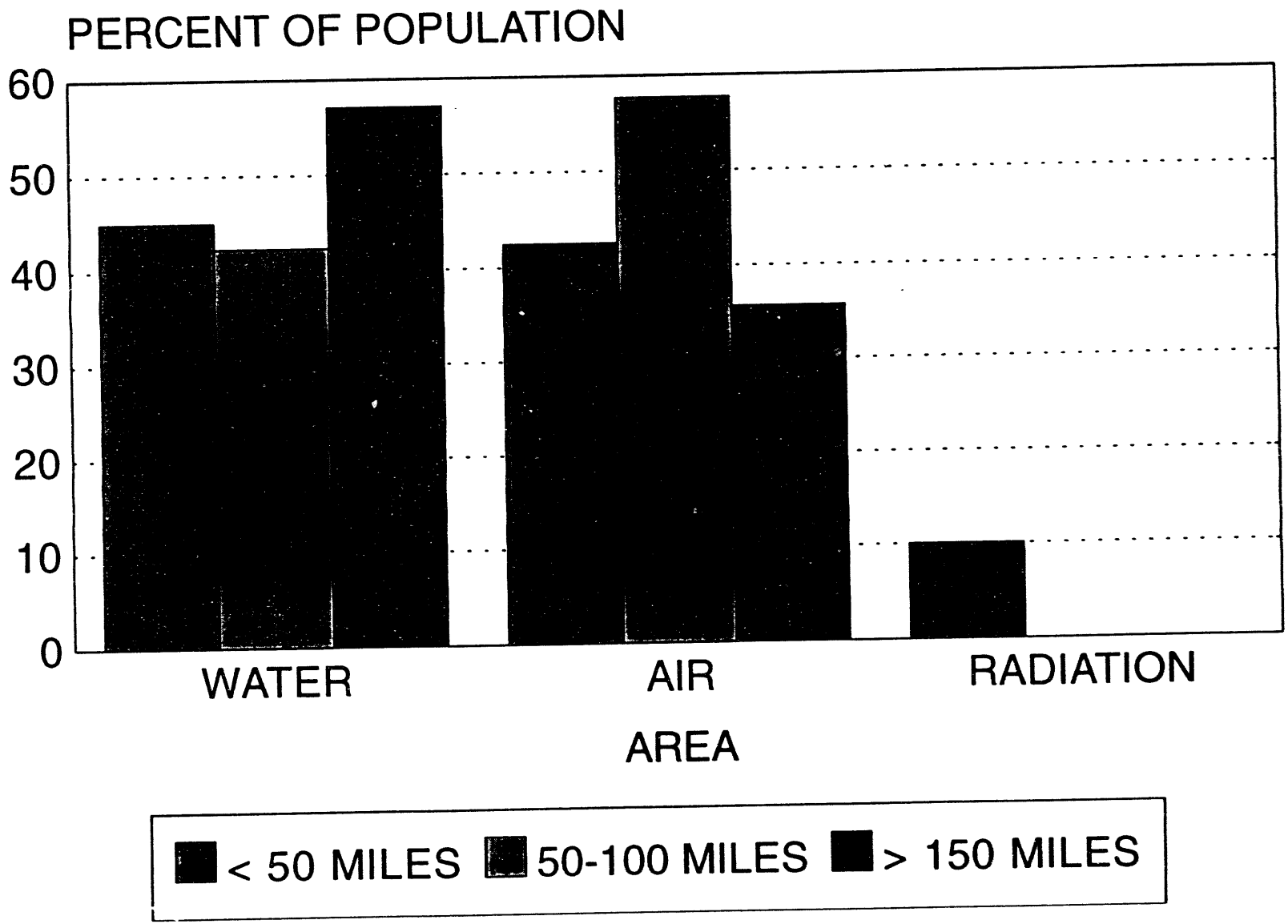
ATTITUDES REGARDING SAVANNAH RIVER SITE



MORTALITY BY GEOGRAPHIC REGION



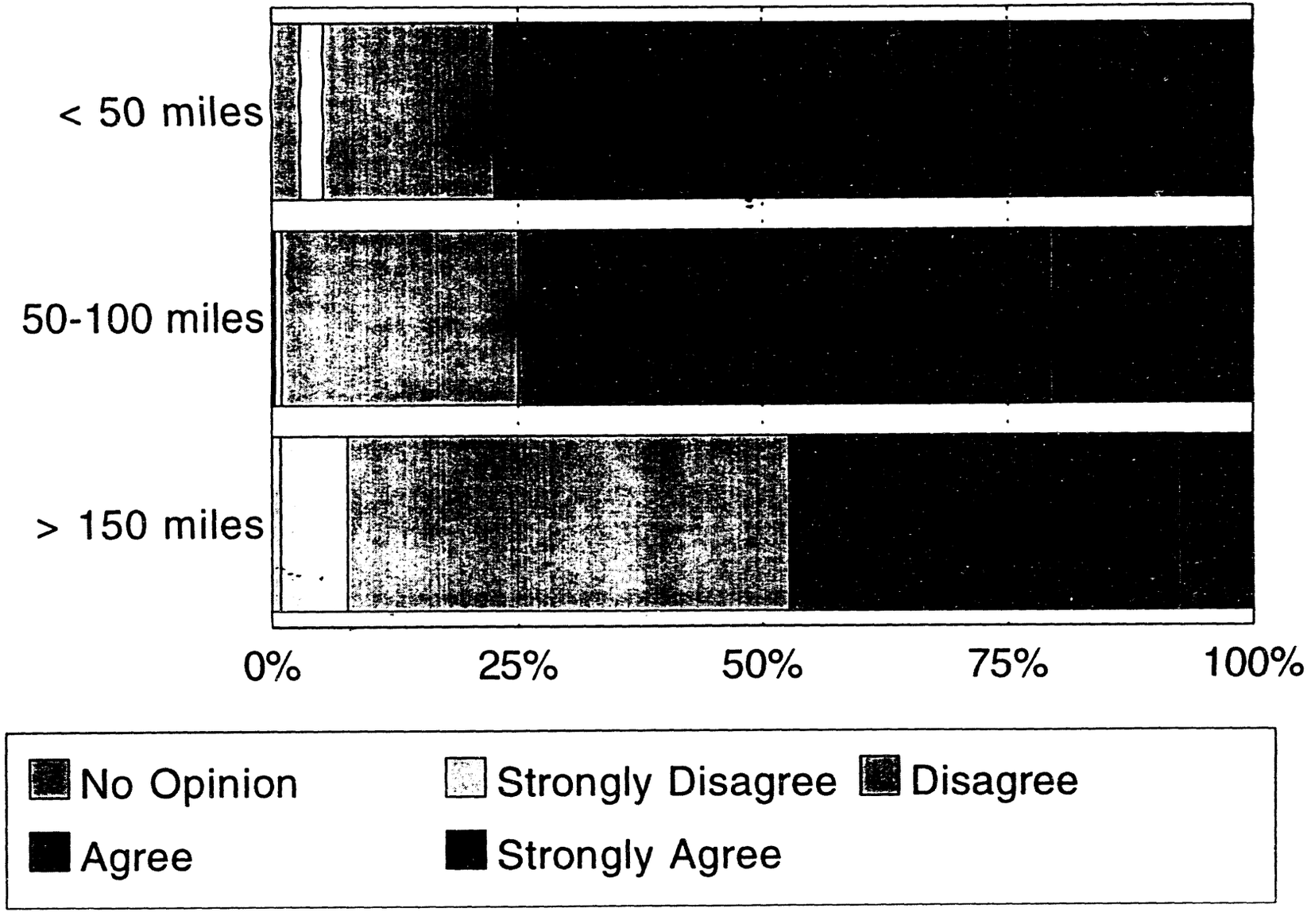
IF GREATER CHANCE OF CANCER, WHAT IS THE MAJOR TYPE OF POLLUTION



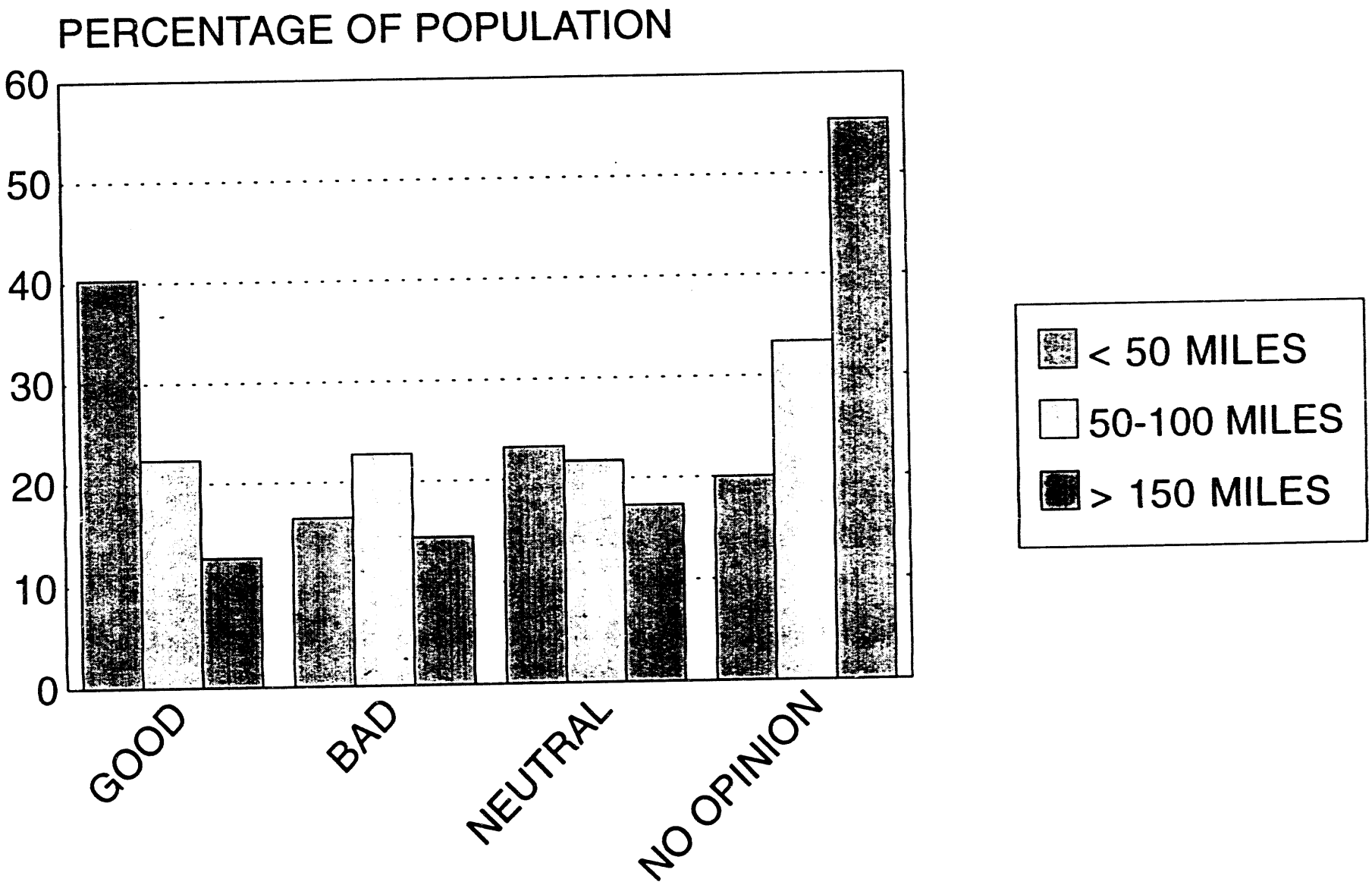
IF LESS CHANCE, WHY LESS LIKELY TO GET CANCER

	< 50 MILES	50-100 MILES	> 150 MILES
LESS POLLUTION	36.8%	71.4%	61.9%
GENETICS	2.6%	2.9%	2.4%
LOW TOBACCO USE	7.9%	2.9%	9.5%
GOOD NUTRITION	0.0%	5.7%	9.5%
OCCUPATION	2.6%	5.7%	2.4%

SHOULD KNOW AS MUCH AS POSSIBLE ABOUT THE CHEMICALS IN THE ENVIRONMENT



ATTITUDES REGARDING SAVANNAH RIVER SITE



INTERNATIONAL CONFERENCE

IMMUNOGENETIC RISK ASSESSMENT IN HUMAN DISEASE

Medical University of South Carolina
Environmental Hazards Assessment Program

Co-Chairs: **Janardan P. Pandey, Ph.D.**
Department of Microbiology & Immunology

David G. Hoel, Ph.D.
Department of Biostatistics & Epidemiology

March 6-8, 1994
Omni Hotel

INTERNATIONAL CONFERENCE ON
IMMUNOGENETIC RISK ASSESSMENT IN HUMAN DISEASE

March 6-8, 1994
Charleston, South Carolina

Sponsors: Medical University of South Carolina

Environmental Hazards Assessment Program

Co-Chairs: **Janardan P. Pandey, Ph.D.**
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David G. Hoel, Ph.D.
Department of Biostatistics & Epidemiology

Speakers and topics:

J. F. Crow, Ph.D. (*Univ. Wis.*)—Spontaneous Mutation as a Risk Factor

R. Elston, Ph.D. (*LSU*)—Association and Linkage to Genetic Markers

C.I. Amos, Ph.D. (*M.D. Anderson, Texas*)—Major Gene Analysis

R. Grubb, M.D., Ph.D. (*Sweden*)—Recent Advances in Immunoglobulin Genetics

E. Yunis, M.D. (*Harvard*)—Recent Advances in MHC Genetics

C. Alper, M.D. (*Harvard*)—Genetic Control and Cellular Mechanisms in teh Immune Response to HB_sAG

F. Miller, M.D., Ph.D. (*NIH*)—Immunogenetics of Autoimmune Diseases

D. Hafler, M.D. (*Harvard*)—MHC-Restricted Recognition of Autoantigens

C.R. Cloninger, M.D. (*Wash. U.*)—Genetic Risk Assessment in Psychiatric Diseases

D. Propert, Ph.D. (*Australia*)—Immunoglobulin Allotypes and RFLPs in Disease Association

F. Black, Ph.D. (*Yale*)—Immunogenetics of Infectious Diseases

T. Sasazuki, M.D. (*Japan*)—Regulation of Immune Response and Disease Susceptibility by Interaction of the Genes within HLA Multigene Family

J. P. Pandey, Ph.D. (*MUSC*)—Immunoglobulin Allotype-Associated Immune Responsiveness

C. Langley, Ph.D. (*UC Davis*)—Genetic Hitchhiking

R. Grubb, M.D., Ph.D. (*Sweden*)—Perspectives and Future Directions

CONFERENCE THEME

1) Recent advances in HLA and immunoglobulin genetics;

2) The role of HLA and immunoglobulin allotypes in immune responsiveness to certain antigens;

3) Associations of HLA and allotypes with susceptibility/resistance to various diseases; and

4) Biometrical methods employed in such investigations.

MEDICAL UNIVERSITY OF SOUTH CAROLINA

MUSC is among the nation's oldest medical institutions and was the first established in the South. Founded in 1824 as the Medical College of South Carolina, its campus now forms the core of the state's largest medical complex.

After gaining university status in 1969, an intense period of construction added a new library, basic science building, clinical science building, the Storm Eye Institute, the Children's Hospital and the Psychiatric Institute. A second major phase brought the addition of a cancer center, student center and sports complex.

Currently in the planning stages is the construction of two new biomedical research centers adding 400,000 square feet.

ENVIRONMENTAL HAZARDS ASSESSMENT PROGRAM

The Environmental Hazards Assessment Program (EHAP) is the Medical University of South Carolina's health-based response to the complex and challenging issues of environmental risk and cleanup.

Recognizing that there is no single solution or outlook applicable to the many problems posed by environmental cleanup, EHAP brings a wide cross-section of affected individuals and groups to the table for open dialogue on the issues.

EHAP simultaneously addresses the issues on many fronts. EHAP research currently includes work in such areas as risk analysis, risk communication, microbiology, immunology and toxicology. In 1993, EHAP's monthly Crossroads of Humanity Series of Round Table Forums and Workshops attracted nearly 100 experts in environment-related fields to Charleston for the purpose of recognizing and addressing the stumbling blocks we encounter on the road to a healthy environment. Also in 1993, the Medical University inaugurated a doctoral program in Environmental Risk Assessment.

With projects in place and more on the way, EHAP has established the Medical University of South Carolina as a place where environmental issues will continue to be raised, discussed, studied and ultimately resolved.

AGENDA

Sunday, March 6, 1994

5:00 pm-7:30 pm **Registration**
Grand Hall

6:00 pm-7:30 pm **Welcome Reception**
Cypress Room

7:30 pm-9:30 pm **Subscription Banquet**
Willow Room

Banquet Program

Introduction **David G. Hoel, Ph.D.**
Department of Biostatistics & Epidemiology
Medical University of South Carolina
Charleston, South Carolina

Greetings **W. Marcus Newberry, M.D.**
Vice President for Academic Affairs and Provost
Medical University of South Carolina
Charleston, South Carolina

Janardan P. Pandey, Ph.D.
Department of Microbiology & Immunology
Medical University of South Carolina
Charleston, South Carolina

Keynote Speaker **James F. Crow, Ph.D.** -- Spontaneous Mutation as a Risk Factor
Department of Genetics
University of Wisconsin
Madison, Wisconsin

Monday, March 7, 1994

8:00 am-5:00 pm **Registration**
Grand Hall

8:30 am-8:40 am **Welcoming Remarks**
Willow Room

David G. Hoel, Ph.D.
Department of Biostatistics & Epidemiology
Medical University of South Carolina
Charleston, South Carolina

James B. Edwards, D.M.D.
President
Medical University of South Carolina

8:40 am-11:40 am **Session I: Biometrical Genetics**
Willow Room

Session Chair:
David G. Hoel, Ph.D.
Department of Biostatistics & Epidemiology
Medical University of South Carolina
Charleston, South Carolina

8:40 Association and Linkage to Genetic Markers

Robert C. Elston, Ph.D.
Department of Biometry & Genetics
Louisiana State University
New Orleans, Louisiana

9:30 am-9:50 am **Intermission**

9:55 Major Gene Analysis

Christopher I. Amos, Ph.D.
M.D. Anderson Cancer Center
Houston, Texas

10:50 Genetic Hitchhiking

Charles H. Langley, Ph.D.
Ctr. for Population Biology
University of California
Davis, California

11:40 am-1:30 pm **Break for Lunch**

1:30 pm-3:10 pm **Session II: HLA, Immune Response and Disease**
Willow Room

Session Chair:
Janardan P. Pandey, Ph.D.
Department of Microbiology & Immunology
Medical University of South Carolina
Charleston, South Carolina

1:35 Recent Advances in HLA Genetics

Edmond J. Yunis, M.D.
Department of Immunogenetics
Sidney Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

2:30 Genetic Control and Cellular Mechanisms in the Immune Response to HB_sAg

Chester A. Alper, M.D.
Center for Blood Research
Harvard Medical School
Boston, Massachusetts

3:10 pm-3:30 pm **Intermission**

3:35 Immunogenetics of Autoimmune Diseases

Frederick W. Miller, M.D., Ph.D.
Molecular Immunology Laboratory
Food and Drug Administration
Bethesda, Maryland

4:30 Regulation of Immune Response and Disease Susceptibility by Interaction of the Genes within HLA Multigene Family

Takehiko Sasazuki, M.D.
Department of Genetics
Medical Institute of Bioregulation
Kyushu University
Fukuoka, Japan

5:25 Immunogenetics of Infectious Diseases

Francis L. Black, Ph.D.
Department of Epidemiology & Public Health
Yale University School of Medicine
New Haven, Connecticut

Tuesday, March 8, 1994

8:30 am-10:20 am **Continuation of Session II**
Willow Room

8:30 MHC-Restricted Recognition of Autoantigens

David A. Hafler, Ph.D.
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

9:30 Genetic Risk Assessment in Psychiatric Diseases

C. Robert Cloninger, M.D.
Department of Psychiatry
Washington University
St. Louis, Missouri

10:20 am-10:40 am **Intermission**

10:40 am **Session III: Immunoglobulin Allotypes, Immune Response and Disease**
Willow Room

Session Chair:
David G. Hoel
Department of Biostatistics & Epidemiology
Medical University of South Carolina
Charleston, South Carolina

10:45 Recent Advances in Immunoglobulin Genetics

Rune Grubb, M.D., Ph.D.
Department of Medical Microbiology
University of Lund
Lund, Sweden

11:35 am-1:30 pm **Break for Lunch**

1:30 Immunoglobulin Allotypes and RFLPs in Disease Association

David N. Propert, Ph.D.
Department of Applied Biology
Royal Melbourne Institute of Technology
Melbourne, Australia

2:25 Immunoglobulin Allotype-Associated Immune Responsiveness

Janardan P. Pandey, Ph.D.
Department of Microbiology & Immunology
Medical University of South Carolina
Charleston, South Carolina

3:15 Perspectives and Future Directions

Rune Grubb, M.D., Ph.D.
Department of Medical Microbiology
University of Lund
Lund, Sweden

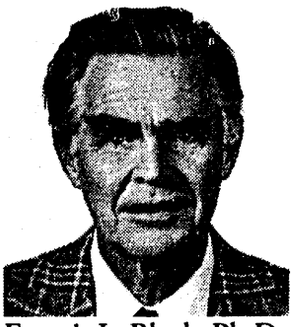
Conclusion **Janardan P. Pandey, Ph.D.**

Chester A. Alper, M.D.

Chester A. Alper, M.D., is a Professor of Pediatrics at Harvard Medical School and a Senior Associate in Hematology and Oncology at the Children's Hospital in Boston. He is a member of the American Association of Immunologists, the American Society for Clinical Investigation and the Association of American Physicians. Dr. Alper holds an A.B. from Harvard College and an M.D. from Harvard Medical School. He has authored more than 200 publications.

Christopher I. Amos, Ph.D.

Christopher I. Amos, Ph.D., is an Associate Professor for the Department of Epidemiology in the Division of Cancer Prevention at the Anderson Cancer Center in Texas. He is also an Associate Adjunct Professor in the Department of Genetics at the Graduate School for Biologic Sciences. He is a member of the International Genetic Epidemiology Society, the American Society of Human Genetics and the American Association of Cancer Research. Dr. Amos holds a B.A. from Reed College and an M.S. and a Ph.D. from Louisiana State University Medical Center.



Francis L. Black, Ph.D.

Francis L. Black, Ph.D., is a Professor of Epidemiology and Head of the Division of Microbiology in the Department of Epidemiology and Public Health at Yale University School of Medicine. His major research interests include studying the role of genetic determinants in the immune response and the population genetics of susceptibility to infectious disease. Dr. Black holds a B.A. and an M.A. from the University of British Columbia and a Ph.D. in Biochemistry from the University of California.

C. Robert Cloninger, M.D.

C. Robert Cloninger, M.D., is a Professor of Psychiatry, Genetics and Psychology at Washington University in St. Louis. His major research interests include alcoholism, schizophrenia, personality disorders and somatoform disorders. Dr. Cloninger holds a B.A. in Philosophy, Anthropology and Psychology from the University of Texas and an M.D. from Washington University. He has authored more than 200 publications.

James F. Crow, Ph.D.

James F. Crow, Ph.D., is a Professor Emeritus at the University of Wisconsin. He has been appointed Chairman of the Committee on DNA Technology in Forensic Sciences for the National Academy of Sciences. Dr. Crow holds a B.A. from Friends University and a Ph.D. from the University of Texas.

Robert C. Elston, Ph.D., is a Professor and Head of the Department of Biometry and Genetics and Director of the Center for Molecular and Human Genetics at Louisiana State University Medical Center. He is a member of the International Society of Psychiatric Genetics, the American Public Health Association and the International Genetic Epidemiology Society. Dr. Elston received his B.A. and M.A. from Cambridge University and his Ph.D. from Cornell University. He has authored more than 300 publications.

Rune Grubb, M.D., Ph.D.

Rune Grubb, M.D., Ph.D., is a Professor Emeritus and Staff Member in the Department of Medical Microbiology for Lund University in Sweden. He is an honorary member of the American Society for Immunology and a member of the Swedish Royal Academy of Sciences. Dr. Grubb holds an M.D. and a Ph.D. from Lund University.

David A. Hafler, M.D.

David A. Hafler, M.D., is an Associate Professor of Neurology at Harvard Medical School and a Physician at Brigham and Women's Hospital. He is a member of the American Neurological Association and the American Society of Clinical Investigation. Dr. Hafler holds a B.S. and an M.S. from Emory University and an M.D. from the University of Miami School of Medicine.

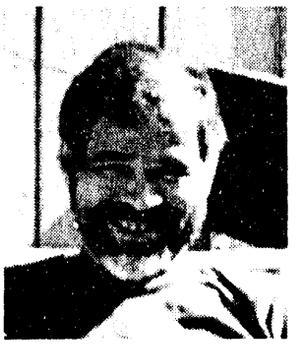
David G. Hoel, Ph.D.

David G. Hoel, Ph.D., is a Professor and Chairman of the Department of Biometry and Epidemiology and Associate Director of the Hollings Cancer Center at the Medical University of South Carolina. He is a member of the National Council on Radiation Protection and Measurement . Dr. Hoel holds an A.B. from the University of California at Berkeley and a Ph.D. from the University of North Carolina at Chapel Hill.

Charles H. Langley, Ph.D., is a Professor of Evolution and Ecology in the Center for Population Biology at the University of California. He has been a research geneticist for over 20 years and has published numerous articles on the subject. Dr. Langley holds a B.A. and Ph.D. in Zoology from the University of Texas.

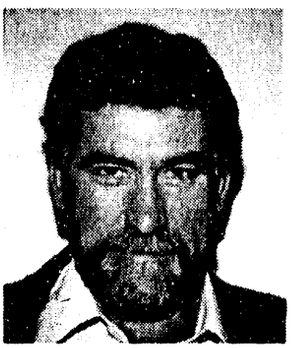
Frederick Miller, M.D., Ph.D.

Frederick W. Miller, M.D., Ph.D., conducts research at the Laboratory of Molecular Immunology for the Division of Cellular and Gene Therapies at the Center for Biologics Evaluation and Research in Maryland. His research interests include studying the genetic and environmental risk factors associated with autoimmunity and epidemiology of environmentally-associated and idiopathic autoimmunity. He is a member of the American Association for the Advancement of Sciences and the American Association of Immunologists. Dr. Miller holds a B.A. from Miami University and an M.D. and Ph.D. from Case Western Reserve University School of Medicine.



Janardan P. Pandey, Ph.D.

Janardan P. Pandey, Ph.D., is a Professor of Immunology in the Department of Microbiology and Immunology at the Medical University of South Carolina. He is a member of the American Association of Immunologists and the American Society of Human Genetics. Dr. Pandey holds an M.S. and a Ph.D. from the University of Wisconsin.



David N. Propert, Ph.D.

David N. Propert, Ph.D., is a Professor in the Department of Applied Biology and Biotechnology at the Royal Melbourne Institute of Technology in Australia. Since 1967, he has been responsible for planning, coordinating and teaching all aspects of higher-organism genetics in his department. Dr. Propert is a member of the Human Genetics Society of Australasia and the Australian Huntington's Disease Association.

Takehiko Sasazuki, M.D.

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Chester A. Alper, M.D.

Genetic control and cellular mechanisms in the immune response to HBsAg

Chester A. Alper, M.D.

A. Murine immune response to HBsAg

* Inbred strains of mice are high, medium, low or nonresponding (Milich et al, 1983. J Immunol 130:1395; Milich et al, 1984. J Exp Med 159:41)
* Response is dominantly inherited and mediated via T helper cells; lack of response is recessively inherited and associated with lack of T cell help (Milich 1989, Human Immunogenetics. Marcel Dekker, NY)
* Control of response in murine H-2 IA and IE (?suppressive) regions but suppression never basis of nonresponse (Milich et al, 1984. J Exp Med 159:41; Milich & Chisari, 1982. J Immunol 129:320; Milich, Louie & Chisari, 1985. J Immunol 134:4194)
* T helper cells from responder (but not nonresponder) mice proliferate in response to HBsAg; nonresponse at level of APC-T cell interaction (Milich 1989, Human Immunogenetics. Marcel Dekker, NY)
* BALB/c proliferative response blocked by anti-I-A^d and anti-IE^d (Milich 1989, Human Immunogenetics. Marcel Dekker, NY)
* Different strains recognize different T cell epitopes on HBsAg (Milich et al, 1985. J Immunol 134:4203)

B. Human immune response to HBsAg

* Antibody response to HBsAg in normal population is at least bimodal with 4% nonresponders, 10% hyporesponders (<1000 RIA U/ml) (Craven et al, 1986. Ann Intern Med 105:356; Alper et al, N Engl J Med 321:708)
* Increase in [HLA-B8, SC01, DR3], [HLA-B44, FC31, DR7], DR3 and DR7 among nonresponders; distribution fits Hardy-Weinberg equilibrium (Craven et al, 1986. Ann Intern Med 105:356)
* In prospective immunization of homozygotes and heterozygotes for [HLA-B8, SC01, DR3], homozygotes made much less antibody than heterozygotes
* T cell proliferative response in vitro parallels antibody response in vivo; Removal of $CD8^+$ cells doesn't convert nonresponder to responder (Egea et al, 1991. J Exp Med 173:531)
* Immunodominant T cell epitope is p139-146; T cell proliferation more or less comparable to whole HBsAg. Anti-DR (not anti-DQ or anti-DP) blocks proliferative response to HBsAg and p139-146 (Deulofeut et al, 1993. Mol Immunol)
* Defect in nonresponders in T cells, not in APC or MHC class II binding (Salazar et al, 1994, submitted for publication)
* Family studies of HBsAg response show dominant response, recessive nonresponse; response linked to MHC with lod score >6.0; one pair of MHC-identical sibs discordant for response (Kruskall et al, 1992. J exp Med 175:495)
* Most, but not all, homozygotes for [HLA-B8, SC01, DR3] and [HLA-B44, FC31, DR7] are nonresponders (Unpublished observations)

Thus, human anti-HBs nonresponse recessive, response dominant. Nonresponse due to absence of help, not presence of suppression, either $CD8^+$ cells, TH2 cells or inhibitory cytokines. Defect resides in T cells

Christopher I. Amos, Ph.D.

MAJOR GENE ANALYSIS FOR DISEASES AND DISORDERS OF COMPLEX ETIOLOGY

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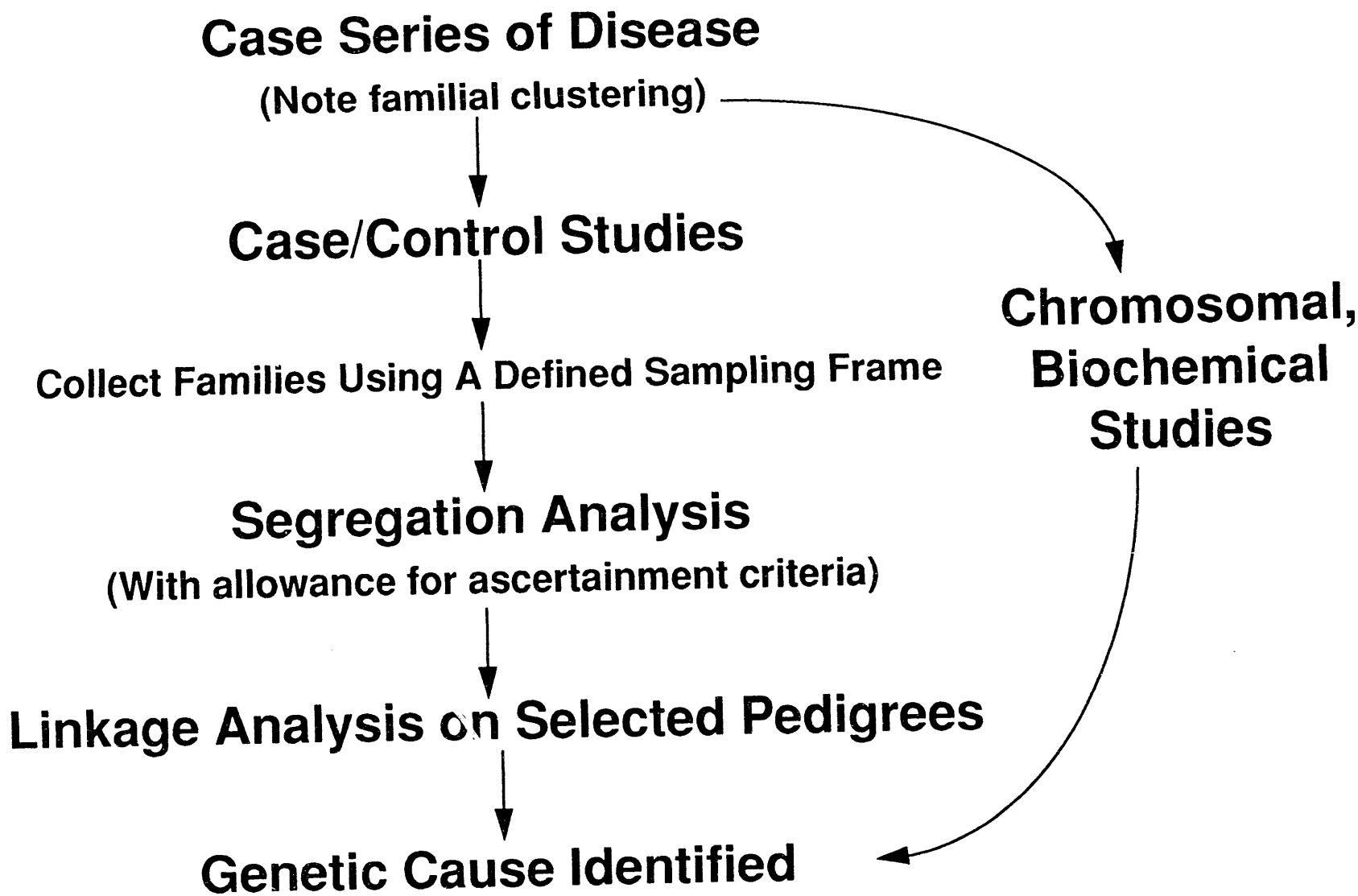
Purposes of Genetic Studies

- Document Genetic Effects on Susceptibility to Disease or Interindividual Variation in a Trait
- Localize Major Genes to Chromosomal Region
- Obtain More Precise Estimates of Genetic and Environmental Components of Disease Risk

"Classic Paradigm" for Isolating Genetic Effects in Disease Causation



New Paradigm for Isolating Genetic Effects in Disease Causation

Case Series of Disease

↓

Linkage Analysis on Selected Pedigrees

↓

Modeling of Segregation Parameters

↓

Genetic Etiology Identified

↓

Case - Control Studies using Candidate Genes

Variance-Components Tests for Linkage

- Model-free test for linkage
- Provides estimates of heritability directly
- Can be used to estimate θ directly
- Easily incorporates covariates (Environmental effects)
- More powerfully uses pedigree data

Biases in θ from an Incorrect Genetic Model

No Linkage

- No excess in θ false positives if marker model correct
- Possible false positives if many missing individuals, wrong marker frequencies and selection through affected individuals

True Linkage

- Decreased power, likely false negatives and exclusions
  - » Upward Bias in θ if Penetrance is too high
  - » Upward Bias in θ if Genetic Heterogeneity ignored
  - » Downward Bias in θ if Sporadic Risk is too high
  - » Downward Bias in θ if Polygenic Effects ignored

Major Gene Analysis for Diseases and Disorders of Complex Etiology.

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Introduction:

Major gene analysis for complex disorders is undergoing a metamorphosis. The paradigm shift in approaches for major gene analysis stems from the extensive resources now available for DNA marker typing, and in some cases DNA analysis of candidate genes and advances in computational resources which facilitate modeling. Although the purposes for major gene analysis remain the same, the disorders that are being studied are increasingly complex in etiology, and the tools are increasingly precise. Here, I discuss the new order in genetic analysis, and provide an analytic example of the gain in efficiency from using linked genetic markers in a major gene analysis. I then provide an example of the use of a linked marker for the genetic analysis of Ankylosing Spondylitis.

The main focus in major gene analysis is to identify the mechanism by which genetic factors influence disease risk and the population frequency of these factors. A major gene can be tautologically defined to be any specific genetic effect that is detectable by genetic analysis. Risk for complex disorders is typically dependent upon environmental, lifestyle and genetic factors. The parameters of interest for studies for major gene analysis are provided in table 1. The penetrance is defined to be the probability that an individual with a susceptible genotype will become affected by a disease, and estimating this penetrance is a critical concern for major gene analyses. We define the sporadic risk to be the probability that an individual with the nonsusceptible genotype nevertheless becomes affected by the disease. Throughout this manuscript, I have assumed, for simplicity, a biallelic disease locus. For the dominant conditions considered, I have also dropped genotype-specific indices and represent penetrance among individuals carrying at least a single disease-susceptibility allele as f, and

the sporadic risk among those not carrying a susecptibility allele as r. We are also usually interested in estimating the frequency of susceptibility alleles in the general population.

For complex disorders, variation at several genetic loci may affect the risk for disease. An oligogenic model is one in which several disease-susceptibility loci affect the risk for disease. Depending upon the tools that are available, and the sampling strategy, effects from these separate genetic factors may be separately identified. For complex disorders, tools to evaluate oligogenic versus major gene models are needed.

The usual paradigm for the genetic analysis of diseases follows the stages outlined in Figure 1. Typically clinical observations in the form of case series suggest familiality of a disease or trait. These case-series are followed by case-control studies, which provide evidence for familial clustering of the disease, and seek to evaluate epidemiologic risk factors vis-a-vis familial risk for disease. However, these studies typically collect little or no information from the relatives of the index cases, so that possible effects from shared familial environments are usually impossible to evaluate in this design. For these designs the usual unit of observation is the individual case or control. As in most epidemiologic endeavors, sampling strategies and modeling approaches are not heavily model-dependent and the usual estimate of risk that is provided is an odds ratio. Familial or genetic factors are often major confounders in determining risk, and the failure of many epidemiologists to consider genetic effects in their analyses can lead to underestimation of environmental effects on disease risk, and the construction of incorrect significance levels.

In order to model, more precisely, the familial and genetic factors affecting disease expression, case-control studies are followed by segregation analysis. Under the classic paradigm, segregation analytic studies require scrupulous definition and attention to the ascertainment criteria. For the majority of diseases, the occurence of genetic susceptibility is sufficiently uncommon that selection without reference to disease status would result in low power to detect genetic effects. However, most patterns of selection introduce biases into the genetic analyses. When the selection or ascertainment events are well characterized these biases can often be accomodated by appropriate mathematical conditioning. For segregation analysis, the units of observation are individuals within families, and the modeling process, though applied to individuals also requires information on their close relatives. Thus, the unit of sampling and anlysis in segregation analysis is the family. Summary statistics from segregation analytic studies include the gene frequency of the disease-causing locus, penetrance for the susceptible genotypes, and the sporadic risk for the nonsusceptible genotypes. During segregation analysis, the parameters describing the penetrance and the gene frequency are inferred using maximum likelihood methods. The parameters that most accurately describe the observed data are identified by a numerical search. To allow for the variable size and structure of human families, very general algorithms were developed, largely as a result of seminal works by Dr. Elston and colleagues.

Following the usual paradigm for genetic studies, genetic linkage studies are implemented once evidence for major gene inheritance has been provided and a genetic model has been defined by segregation analysis. Results from genetic linkage studies can provide definitive evidence for major gene effects upon disease susceptibility, and also provide an

approximate location for subsequent positional cloning strategies. In genetic linkage studies, the coinheritance of inferred disease susceptibility with genetic markers is evaluated. The observations consist of the disease status and marker values of related individuals in families while families are the sampling units. Ideally, the unit of analysis becomes the separable meiotic events which contain information concerning the recombination fraction. In practice, the unit of analysis often remains the family, because the meiotic events cannot be uniquely determined and family members provide information about the marker-disease haplotypes. Provided a model for the joint effects from 2 disease susceptibility loci is available, perhaps from population studies or by analogy with animal models, genetic linkage analysis assuming a two locus model is currently feasible.

When a candidate locus is identified, then association studies become a powerful tool for modeling genetic parameters. For these analyses, the unit of analysis is the individual. However, sampling through families may be statistically efficient, in which case specialized statistical methodologies are required to allow for the dependence not due to the candidate gene among family members for disease susceptibility.

The usual paradigm for genetic analysis is being replaced because of inherent difficulties in classic segregation analysis. Ascertainment correction is often problematic. Usually, a specialized sampling scheme with rigorous constraints must be implemented to permit collection of data that can be subjected to ascertainment corrections. Although these designs have been implemented and have contributed extensively to our knowledge of cardiovascular diseases and common cancers such as breast and lung cancers, these designs

can be prohibitively expensive to implement. Typically, families are most easily identified and most willing to participate when they contain several affected individuals, but constructing a well defined sampling scheme from this highly selected subset of willing participants is impossible. For the purposes of genetic linkage analysis, which provides definitive evidence for a major genetic influence, families selected for segregation analysis usually provide little information. Families that contain many affected individuals provide the greatest information for genetic linkage studies of complex disorders, but these families are usually rare in samples obtained from segregation analytic studies. Under the classic paradigm, linkage studies require parameter estimates from segregation analysis or other population studies. Because different samples are required for segregation and linkage analyses, and the genetic causes for diseases may be heterogeneous, results from the requisite segregation analyses may not represent the families required for subsequent linkage studies. Finally, for complex disorders, multilocus models should be considered in segregation analysis, but numeric evaluation of the data is problematic, and identifying all of the parameters may not be possible. The models that can be identified by classic segregation analytic strategies are therefore too simplistic to adequately describe most complex disorders.

Because identifying the correct genetic model through segregation analysis is often difficult or impossible, many investigators guess a genetic model, and then test for genetic linkage, without performing any preliminary segregation analysis. This approach has been shown ***not*** to lead to excess false positives, provided the guessing is done prior to any analysis. However, guessing a model and then performing linkage analysis can lead to a dramatic loss in power to detect a true genetic linkage, and leads to a biased estimate of the

recombination fraction, so that this method cannot be used to initiate positional cloning studies. Moreover, only the most noble of investigators can resist some preliminary looks at the data to choose an optimal model for linkage studies.

A new paradigm for genetic studies:

New paradigms, as shown by figure 2, are being developed for studies to identify the genetic parameters that describe the penetrance and population frequency of disease-susceptibility loci. These paradigms result from the recognition that the penetrance parameters can be estimated, without bias, through genetic linkage analysis, and in deference to the beleagured investigator who, having collected scores of families that include many individuals wishes to use the available data optimally. The testing and estimation procedures that are being developed are summarized in table 2, along with the advantages and disadvantages of these new methodolgies.

According to this paradigm, case series still document the presence of familiality for a disease. However, these case-series provide an immediate resource for subsequent genetic linkage studies, which would be followed by segregation analysis. The guess lod score approach, under which the investigator guesses one, or, at most, a handful of possible genetic models to describe the observed data is applied to evaluate possible evidence for genetic linkage. In the event that a few genetic models are tried in the preliminary genetic linkage analysis, allowance for multiple tests through use of the Bonferroni correction (which multiplies the significance by the number of tests) would be needed to ensure that the

analysis-wise significance remained constant, and that LOD scores obtained from this type of exploratory analysis can be compared with LOD scores from studies which have used a single genetic model. Investigators who are loathe to apply genetic modeling strategies at this stage may instead use model-free approaches. These approaches have the advantages of being simple to apply, and also do not entail the loss of power in the correction for multiple tests which would be necessary for model-dependent procedures.

Provided some evidence for genetic linkage is obtained, the investigator may then want to collect further families and/or perform additional modeling of the disease process. In many cases preliminary linkage studies can provide insights into the likely inheritance pattern for the disease process, and thereby can result in constructing a more efficient sampling strategy for subsequent major gene analytic studies. If the disease is sufficiently common, sampling schemes which are applicable for segregation studies can be applied with the aim of performing joint segregation and linkage studies. For rarer diseases, families cannot be obtained through population-based sampling. Instead, families are likely to be available only through self-referral or through registries. However, provided there is genetic linkage between disease susceptibility and a marker locus, these highly selected families can still be used for major gene analysis. In this case, the "MOD" score approach (Greenberg, Hodge and Elston) which consists of maximizing the LOD score over the major gene parameters and the recombination fraction has been shown to correct for any ascertainment scheme and provide unbiased estimators of both the major gene effects and the recombination fraction. Families selected for genetic linkage studies can be expected to provide an excellent resource for subsequent positional cloning approaches. A final step in this paradigm remains association

studies, using the cloned candidate gene to assess individual-specific susceptibility.

Efficiency comparisons from the use of a linked genetic marker.

Although joint segregation and linkage analysis can be expected to provide improved efficiency over segregation analysis alone, no studies are available to indicate the gain from use of the linked marker in the analysis. In table 3, I provide probabilities and information functions for estimating the penetrance of a dominant condition for phase-unknown sib-pairs from a double backcross mating. The information functions are the reciprocal of the asymptotic variance of the penetrance estimator and were calculated from the probabilities as summarized in Ott (1991). In addition to including a parameter for decreased penetrance, which is denoted by f, I have also included a parameter to model the sporadic risk for occurrence of the disease, which is denoted by r. In order to simplify the expressions, I have assumed that the affected parent carries a single copy of the susceptibility allele, and the unaffected parent is not susceptible. As shown by figure 3, the variance of the penetrance estimator decreases with decreasing recombination fraction between a marker and a disease-susceptibility locus, with the sporadic risk considerably affecting the variance at all values of the penetrance. As shown in figure 4, a dramatic gain in efficiency, as measured by the ratio of the variance of the linked (recombination fraction = 5%) versus an unlinked (recombination=0.5) marker, is obtained for most values of the penetrance and sporadic risk. An exception is the pathological case when the sporadic risk and the penetrance are equal, when inclusion of linkage information does not improve the estimation of the penetrance parameter. As shown by figure 4, for disorders of low penetrance, a great gain of efficiency

occurs when a linked genetic marker is used in the analysis, again provided the penetrance is substantially higher than the sporadic risk.

In this analysis, I have assumed that one parent is a gene carrier for the susceptibility allele, while the other is not. I have also assumed that selection is through the affected parent, so that no ascertainment correction was needed. The assumption that selection through an affected parent leads to double backcross matings is only valid for rare susceptibility alleles, with a low sporadic risk. Allowing for the sporadic risk in the selection process lead to considerably more complex information functions. Generally, if selection of the sample leads to inclusion of a large number of sporadic cases, the information about the penetrance is considerably reduced, and one finds a minimal change in the relative efficiencies.

Major Gene Methods for Segregation Analysis Using Linked Markers.

The development and application of the mixed model, which includes estimation of a major gene and polygenic effects, has been the subject of extensive controversy. Although this model is generally preferred by geneticists as adequately modeling many disorders of complex etiology, it is numerically impossible to implement except for the smallest of human pedigrees. As a result, several alternative strategies have been developed to model the familial dependence that results from inheritance of genetic factors that may have relatively small effect upon the risk for disease. An excellent approach consists of replacing the exact numerical integrations with an approximation of the cumulative normal distribution, and this

approach has been implemented by Sandra Hasstedt in her program PAP (Hasstedt et al). This program is extremely flexible, can easily incorporate a linked marker, as well as limited information about covariate effects. The programs can be optimized over the penetrance parameters, so that either combined linkage and segregation or maximization of the LOD score can be used to estimate the major gene parameters. This program is not user friendly, requires some preliminary processing of pedigrees, and also some FORTRAN knowledge, but it is the most flexible analytic method currently generally available for genetic analysis.

The regressive models, which have been developed by numerous investigators including George Bonney and Robert Elston, model the dependence from familial influences by a sequential conditioning argument. Conditional on the major gene influences, affection of a relative can also affect an individual's risk for affection in this modeling strategy. In its general form, this approach also offers excellent approximations to the full mixed model, and can more easily accomodate effects from epidemiological risk factors. Unfortunately, programs for combined linkage and segregation analysis or for maximizing the lod score over the penetrance parameters are not generally available. A series of programs, Statistical Analysis for Genetic Epidemiology, is available from LSU, but these will only perform linkage analysis according to the old paradigm, in which the genetic model must be fixed prior to analysis. The program LINKAGE has been modified and released in a very limited fashion as REGRESS (Borecki et al, Bonney et al) to permit joint segregation and linkage analysis. However, this program is not fully supported by its authors, and optimization of the likelihood requires an approximately correct choice of initial values. In addition, the optimization routine tends to crash unless only a few parameters are estimated.

Model Free Methods for Major Gene Analysis.

Less heavily model-dependent methods are being developed for application in linkage analysis. These methods can provide estimates of the recombination fraction and also provide limited information about the expression of the major genetic factors. My recent studies concerned implementation of a limited variance-components approach for genetic analysis. This approach requires, as a preliminary step, the calculation of identity by descent sharing among all pairs of relatives in a pedigree. Once this has been identified, the inter- and intraindividual variability is partitioned into components attributable to a major genetic factor that is linked to the marker locus, genetic effects from unlinked loci or polygenic factors, and nongenetic influences. In table 4 the parameters describing the covariance among pairs of individuals in a pedigree, conditional on the marker identity-by-descent sharing is provided. As can be seen, provided at least two unique sets of individuals are included in the analysis, the variance component for the additive major genetic component of variance and the recombination fraction can be identified. The additive component of genetic variance is a function of the penetrance and sporadic risk and the gene frequency of the susceptibility alleles. This variance-components procedure is computationally easy to apply, can include information from environmental covariates, and can be extended to include multivariate effects. Simulation studies of this approach applied to a quantitative trait locus showed that a test for genetic linkage with the appropriate size could be constructed, but the variance components tend to be generally underestimated. Thus, this procedure provides a valid preliminary assessment for a major gene effect and the general locale of this major gene, but further modeling would generally be needed to identify the major gene parameters. Finally,

in application to data, the variance-components approach, or the related Haseman-Elston approach showed greater power in the preliminary detection of linkage than segregation analysis followed by linkage analysis.

Major gene studies of Ankylosing Spondylitis.

The overwhelming association of Ankylosing Spondylitis and the HLA B-27 allele, with an odds ratio of about 80 among Caucasian populations, has been noted for 20 years (Brewerton et al, 1973; Schlosstein et al, 1973).. The frequency of the disease varies among populations in direct proportion to the frequency of HLA B-27. Moreover, transgenic rats transfected with HLA B-27 alleles were shown to develop an arthropathy with extrarticular features similar to those associated with ankylosing spondylitis, although the clinical syndrome in this rat model is similar to Reiter's syndrome, a reactive spondyloarthropathy that is also associated with HLA B-27 (). All of these observations strongly suggest that HLA B-27 is either a causal factor in the etiology of Ankylosing Spondylitis, or is extremely tightly linked to such a causal factor. Nevertheless, previous family studies have found no evidence for linkage between AS and the class I HLA loci. Because families that include several AS affected individuals are rare, it is possible that absence of genetic linkage suggests that the population association between B27 and AS reflects a causal relationship for nonfamilial AS, but the familial cases result from some other causal factor. Alternatively, the association between AS and HLA-B27 might be ascribed to population stratification or other demographic factors that can induce noncausal associations between a disease and a genetic marker. However, these demographic factors generally result in weak associations, with

relative risks under 5 except in the most pathological of situations. Two final possibilities can explain absence to find genetic linkage even when an association is noted. First, the effect of the genetic factor may be weak enough that detecting genetic linkage is difficult without very large sample sizes (Greenberg, 1993). Second the genetic model that was used may be incorrect, thus leading to decreased power to detect a true genetic linkage.

In order to test for genetic linkage and search for genetic factors influencing risk for AS, my colleague Dr. Laurence Rubin at the Womens Hospital in Toronto has been collecting families that include several AS affected individuals for a number of years. Figures 5 and 6 present some of these families. Proband status is known for only about half of the families. Moreover, these families were selected to contain multiple affected individuals, so secondary probands would need to be indicated to provide a sample adequate for classic segregation analysis. The large family from Newfoundland was ascertained because of a high prevalence of the disorder in the village studied. In this case, the ascertainment event includes a time-space clustering of disease, and again correction for ascertainment would be difficult, though perhaps not as critical as for the smaller families collected in the Toronto environs.

Genetic linkage analysis was performed on these data using two previously suggested genetic models (Kidd) derived through consideration of population risks and risk for AS among relatives of AS patients. The first genetic model did not include the association between HLA-B27 and AS in deriving the penetrance parameters for AS. The second model incorporated an association between AS and B-27 by including gametic disequilibrium between an AS-susceptibility locus and B-27. Linkage analysis showed significant evidence for genetic linkage between AS and B-27 under the first model with a maximum LOD score of 3.48 occurring at a recombination fraction of 5%. Under the second model, in which the

association between B-27 and AS is accomodated the maximimum LOD score of 7.50 again occurred at 5% recombination. The fact that these LOD scores are maximal at 5% recombination rather than 0% may reflect chance variation in these pedigrees, or relatively poor fit of the penetrance parameters to these data. Both of the models fitted to these data assumed nearly 50% penetrance among heterozygotes.

As shown in figure 6, major gene modeling of the penetrance parameters, assuming the recombination fraction is 0 suggests that a considerably lower penetrance among heterozygotes is more appropriate for these data. Because the ascertainment events are unclear for many families in this study, I choose to model the major gene parameters by maximizing the LOD score over the penetrance parameters. The analyses that are presented are restricted to the population from Newfoundland, but similar results were obtained when all of the families in the study were included. When no allowance was made for the B-27, AS association, the best fitting genetic model, which I have called a quasirecessive model, had a penetrance of 0.995 to homozygous susceptible individuals, and approximately 20% for heterozygous individuals. Results, shown in figure 7, from the model that allowed for the B-27 association indicate that the best fitting model was a simple dominant model, again with a penetrance of about 20% among heterozygous individuals. Because this model assigns individuals with the B-27 allele a higher probability to be susceptible to disease, Figure 7 suggests that the B-27 allele is dominantly acting. Figure 6, however, suggests that additional HLA alleles or linked loci also affected disease susceptibility. Further consideration of the data that were collected indeed showed that individuals who were B27 positive and who also had a B-60 or B-61 allele were at considerably higher risk than those with a B-27 allele and another HLA antigen. Further modeling of these data are now needed to assess the

ameliorating effects of female sex, which has also been noted in these data.

Conclusion:

Major gene analysis of disorders with complex etiology is undergoing a paradigm shift. For many conditions, families that include many affected individuals are easily obtained. On the other hand population-based samples are often difficult to obtain, and moreover contain little information for genetic linkage studies, which are critical for establishing a major genetic effect in the etiology of the disease. When population based sampling using a defined ascertainment scheme is practical, joint segregation and linkage analyses greatly improve the precision of the penetrance estimators. Methods of joint segregation and linkage analysis remain rather primitive but improved methods can be expected. For rarer disorders, population-based studies are impractical, but collecting families through registries or self-referral is often easy. In this case, maximizing the LOD score over the penetrance parameters provides valid estimators of the penetrance and recombination parameters. Finally, for initial evaluation of familial data to identify major gene effects, model free methods have been developed. Methods based upon identity-by-descent sharing in pedigrees can provide estimators of the components of variance and the recombination fraction. The power of these methods to detect a major gene and genetic linkage may be higher for complex disorders than some traditional methods of genetic linkage because of difficulties in correctly specifying the correct penetrance parameters. Evidence for major genetic effects from the application of model-free approaches can be followed by further

genetic modelling by way of either joint segregation and linkage analysis or by maximizing the LOD score over the penetrance parameters. Although still technically difficult to perform, these latter approaches provide efficient estimates of the recombination fraction, and an estimate of the penetrance parameters. Estimates of the recombination fraction become critical in considering the application of positional cloning strategies, while estimates of the penetrance parameters are needed for genetic and medical counseiing and for public health decisions.

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Table 1: Parameters for major gene analysis

Parameter	Symbol	Definition
Penetrance	f_{ij}	Probability of affection among those having an at-risk genotype, ij.
Sporadic Risk	r_{ii}	Probability of affection among those having the not at-risk genotype, ii.
Dominance		If $f_{ij} = f_{ii}$ then i is dominant to j. If i is a rare allele increasing disease risk, then this gene has dominant expression (relative to j).
Gene Frequency	p_i	Probability of carrying the risk allele, i.
Recombination Fraction	θ	Probability of recombination between two genetic loci, measured in centiMorgans.
Efficiency	$Eff_{\theta=0.05}$	The variance of one estimator relative to another. In this example, the variance of f_{ij} assuming no linkage information relative to when a linked marker at θ=0.05 centiMorgans is available.

Table 2: Designs, Sampling Strategies, and Estimators from Commonly Employed Human Genetic Studies for Complex Disorders

Design	Units of Observation	Units of Sampling	Summary Measures
Case-Series	Cases	Cases	Anecdotal Reports of Familiality
Case-Control	Individuals	Individuals	Odds-Ratio for Family History (FH) and Disease
Historical Cohort	Relatives	Individuals	Relative Risk to Relatives of Cases versus Controls from FH
Segregation Analysis	Relatives	Families	Penetrances, gene frequencies, age-at-onset, requires ascertainment correction
Linkage Analysis Guess LOD	Meioses	Families	Recombination Fraction (θ) Between Disease Locus and Markers Unbiased θ estimate if segregation parameters are guessed correctly.
MOD	Relatives	Families	Penetrances, gene frequencies, age-at-onset, θ Does not require ascertainment correction
Combined Segregation and Linkage	Relatives	Families	Penetrances, gene frequencies, age-at-onset, recombination fraction. Ascertainment correction required.
Candidate Gene			
Case-Control	Individuals	Individuals	Odds ratios for disease from alleles of candidate gene
Cohort Studies	Individuals	Individuals	Relative risk for disease to carriers of risk alleles vs. non carriers.

Table 3: Information Functions For Phase-Unknown

Sib Pairs from a Double-Backcross Mating

Mating Type is Dd12 x dd11

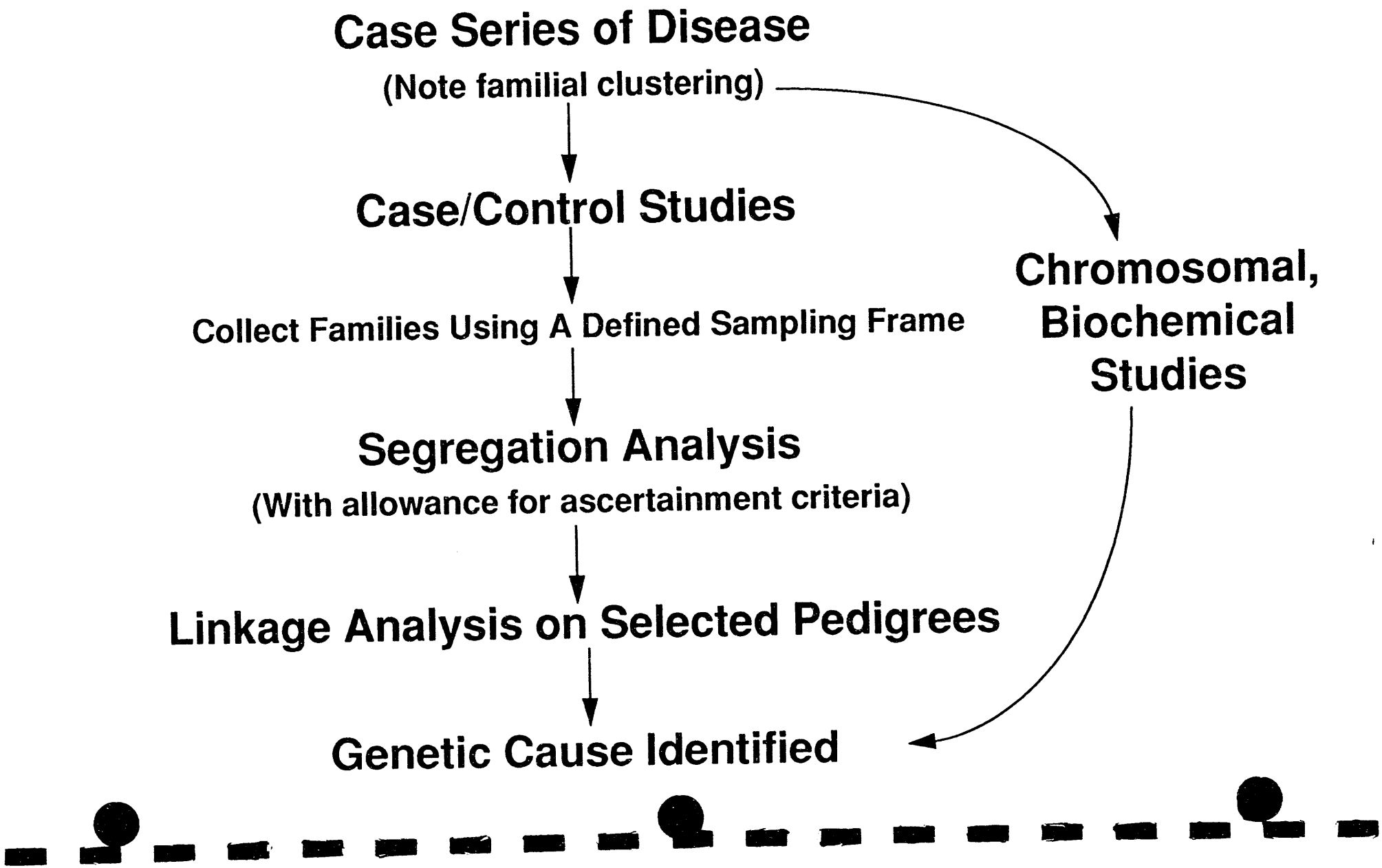
Sib Pairs	*Information*
Dd11-Dd11	$\frac{[(1-\theta)(f(1-\theta)+\theta r)+(\theta(f\theta+r(1-\theta)))]^2}{8\,(f(1-\theta)+\theta r)^2+(f\theta+r(1-\theta))^2}$
dd11-dd11	$\frac{[(1-\theta)((1-f)(1-\theta)+\theta(1-r))-\theta((1-r)(1-\theta)+(1-f)\theta)]^2}{8\,((1-f)(1-\theta)+\theta(1-r))^2+((1-f)\theta+(1-\theta)(1-r))^2}$
Dd11-dd11	$\frac{[(1-\theta)(1-2f(1-\theta)-2r\theta)+\theta(1-2r(1-\theta)-2f\theta)]^2}{4\,(f(1-\theta)+r\theta)((1-f)(1-\theta)+(1-r)\theta)+(f\theta+r(1-\theta))((1-f)\theta+(1-r)(1-\theta))}$
Dd11-dd12	$\frac{[(\theta((1-2r)\theta+(1-2f)(1-\theta))+(1-\theta)((1-\theta)(1-2r)+\theta(1-2f)))]^2}{4\,((1-\theta)(1-r)+(1-f)\theta)(f(1-\theta)+r\theta)+((1-r)\theta+(1-f)(1-\theta))(f\theta+r(1-\theta))}$
Dd12-dd11	$\frac{[(\theta((1-2r)\theta+(1-2f)(1-\theta))+(1-\theta)((1-\theta)(1-2r)+\theta(1-2f)))]^2}{4\,((1-\theta)(1-r)+(1-f)\theta)(f(1-\theta)+r\theta)+((1-r)\theta+(1-f)(1-\theta))(f\theta+r(1-\theta))}$
dd12-dd12	$\frac{[(1-\theta)((1-f)(1-\theta)+\theta(1-r))-\theta((1-r)(1-\theta)+(1-f)\theta)]^2}{8\,((1-f)(1-\theta)+\theta(1-r))^2+((1-f)\theta+(1-\theta)(1-r))^2}$
Dd11-Dd11	$\frac{[(1-\theta)(f(1-\theta)+\theta r)+(\theta(f\theta+r(1-\theta)))]^2}{8\,(f(1-\theta)+\theta r)^2+(f\theta+r(1-\theta))^2}$
Dd11-dd12	$\frac{[(\theta((1-2r)\theta+(1-2f)(1-\theta))+(1-\theta)((1-\theta)(1-2r)+\theta(1-2f)))]^2}{4\,((1-\theta)(1-r)+(1-f)\theta)(f(1-\theta)+r\theta)+((1-r)\theta+(1-f)(1-\theta))(f\theta+r(1-\theta))}$
dd12-dd11	$\frac{[((\theta-1)((1-r)(1-\theta)+(1-f)\theta)-\theta((1-f)(1-\theta)+(1-r)\theta))]^2}{2\,((1-f)(1-\theta)+(1-r)\theta)((1-r)(1-\theta)+(1-f)\theta)}$
DD12-DD11	$\frac{[(1-\theta)(\theta f+(1-\theta)r)+\theta((1-\theta)f+\theta r)^2}{2\,((1-\theta)f+\theta r)(\theta f+(1-\theta)r)}$

Table 4: Monogenic Components of Variance

Relative Pair	*Component of Variance*
Sibs	$[\frac{1}{2} + (1-2\theta)^2(\pi_{ij} - \frac{1}{2})]\sigma_a^2$
Half-Sibs	$[\frac{1}{4} + (1-2\theta)^2(\pi_{ij} - \frac{1}{4})]\sigma_a^2$
Avuncular	$[\frac{1}{4} + (1-2\theta)^2(1-\theta)(\pi_{ij} - \frac{1}{4})]\sigma_a^2$
Grandparental	$[\frac{1}{4} + (1-2\theta)(\pi_{ij} - \frac{1}{4})]\sigma_a^2$
First Cousin	$[\frac{1}{8} + (1-2\theta)^2(1 - \frac{4}{3}\theta + \frac{2}{3}\theta^2)(\pi_{ij} - \frac{1}{8})]\sigma_a^2$

Figure 1

"Classic Paradigm" for Isolating Genetic Effects in Disease Causation



New Paradigm for Isolating Genetic Effects in Disease Causation

Case Series of Disease

↓

Linkage Analysis on Selected Pedigrees

↓

Modeling of Segregation Parameters

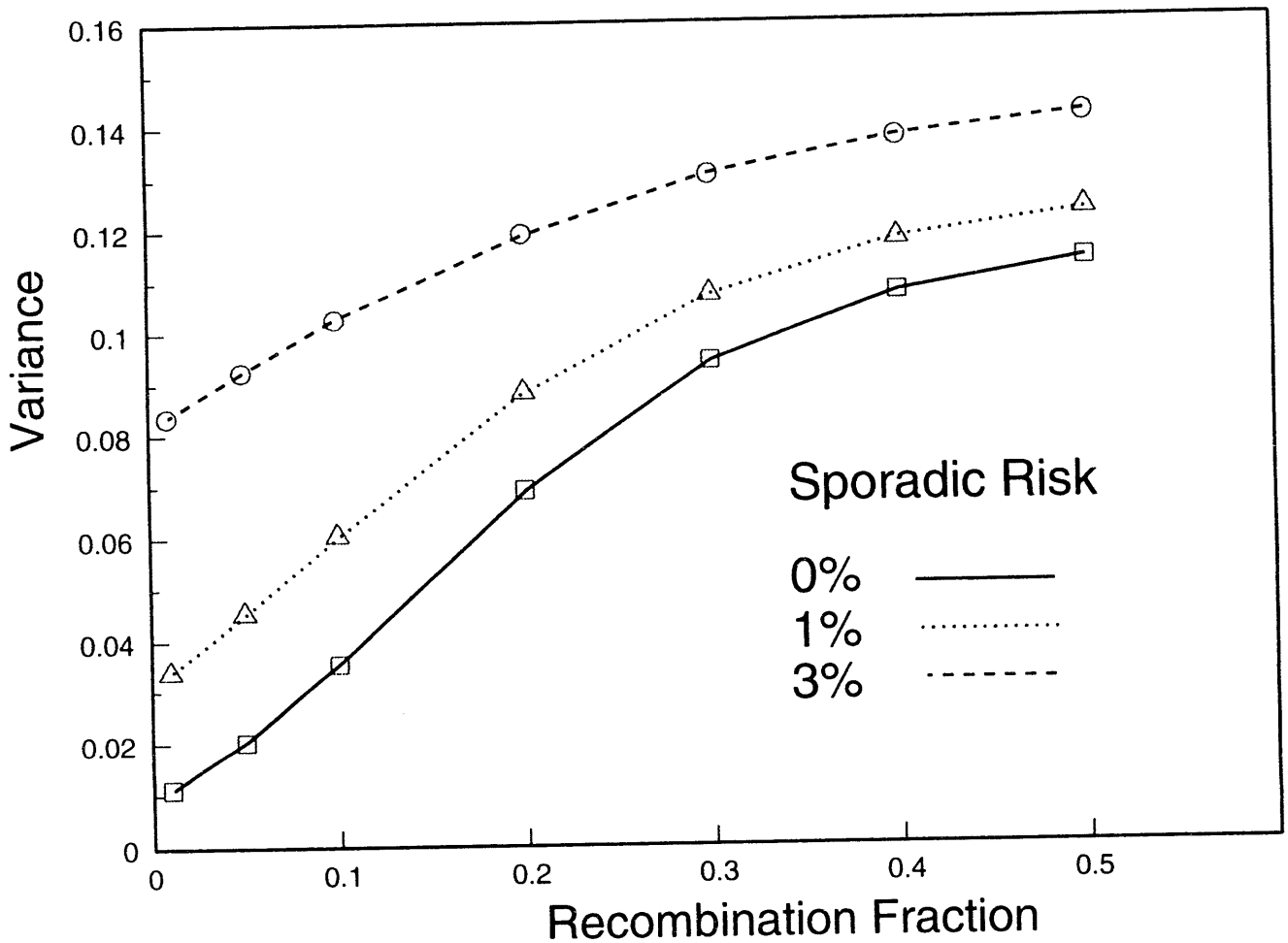
↓

Genetic Etiology Identified

↓

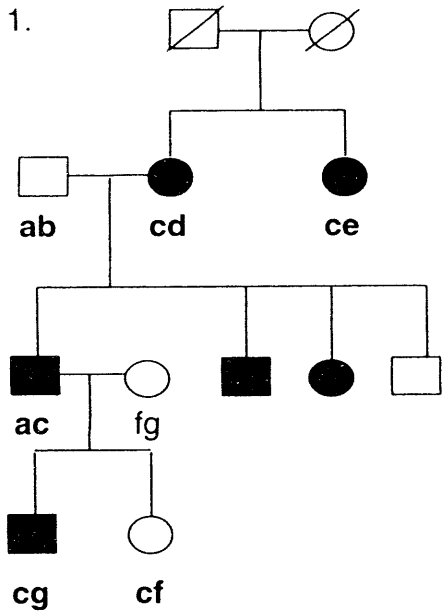
Case - Control Studies using Candidate Genes

Variance of the Penetrance Estimate
Penetrance is 30%



Ankylosing Spondylitis in Toronto Families

1.



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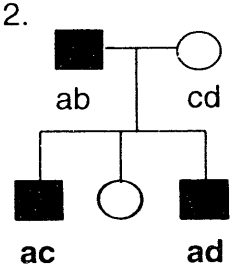

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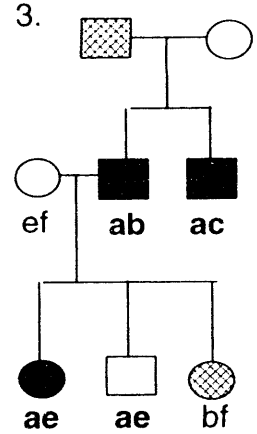

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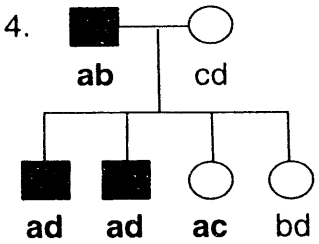

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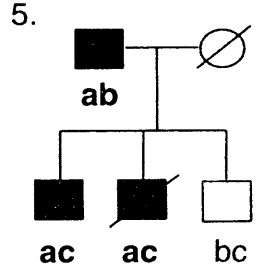

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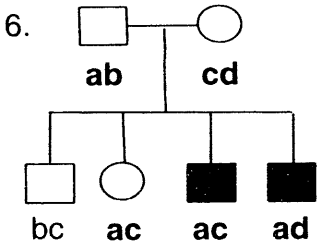

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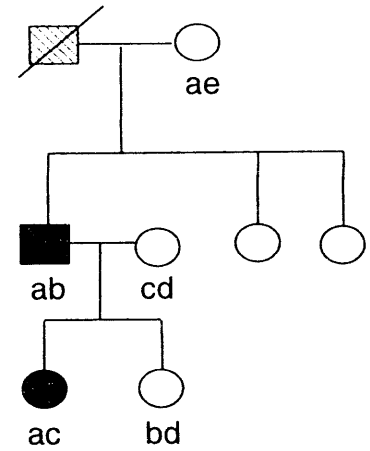


8.

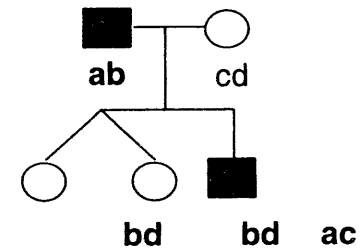


Figure 5. Ankylosing Spondylitis in a Newfoundland Pedigree

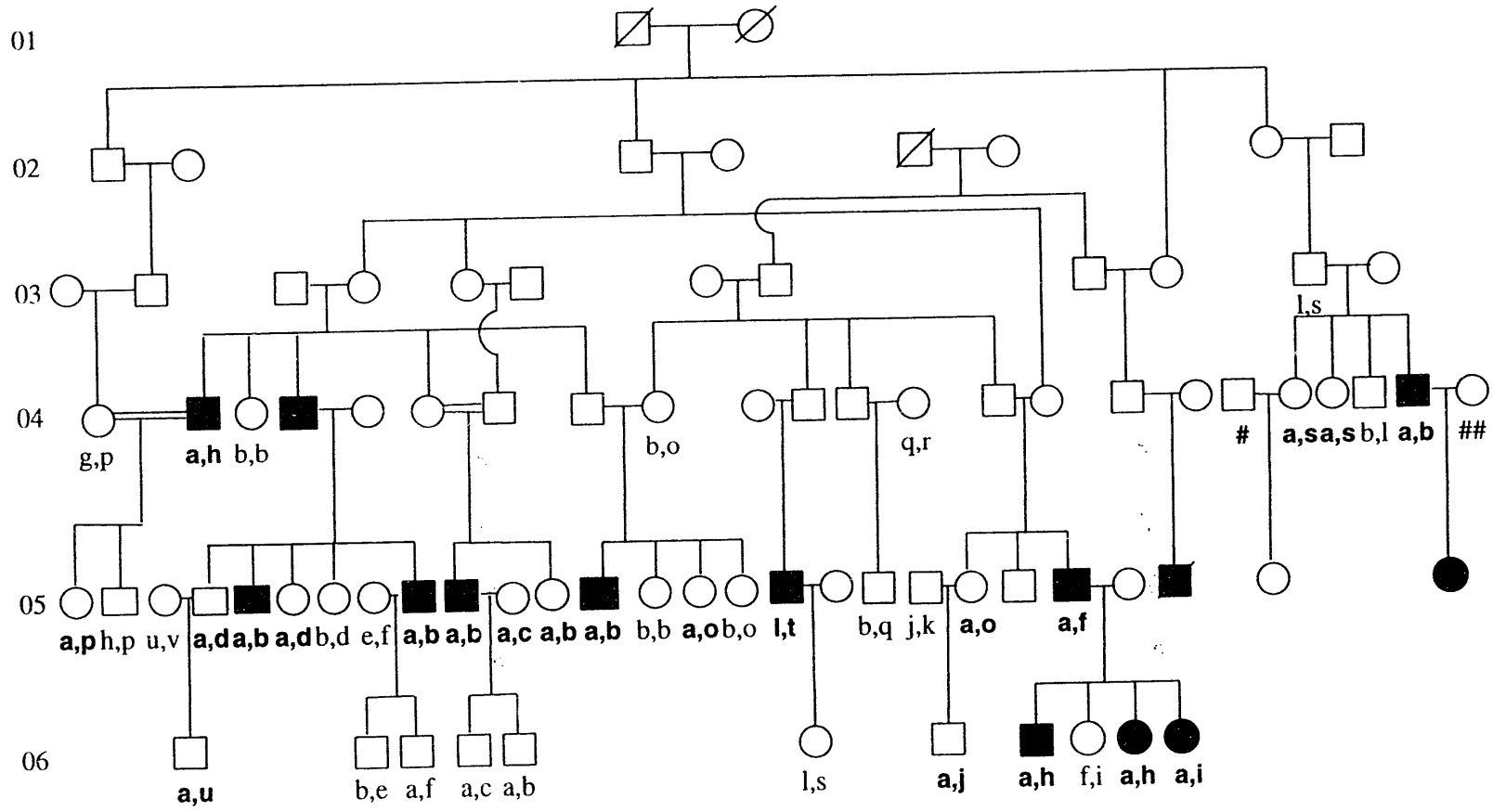


Figure 6: Penetrance versus Lod Score

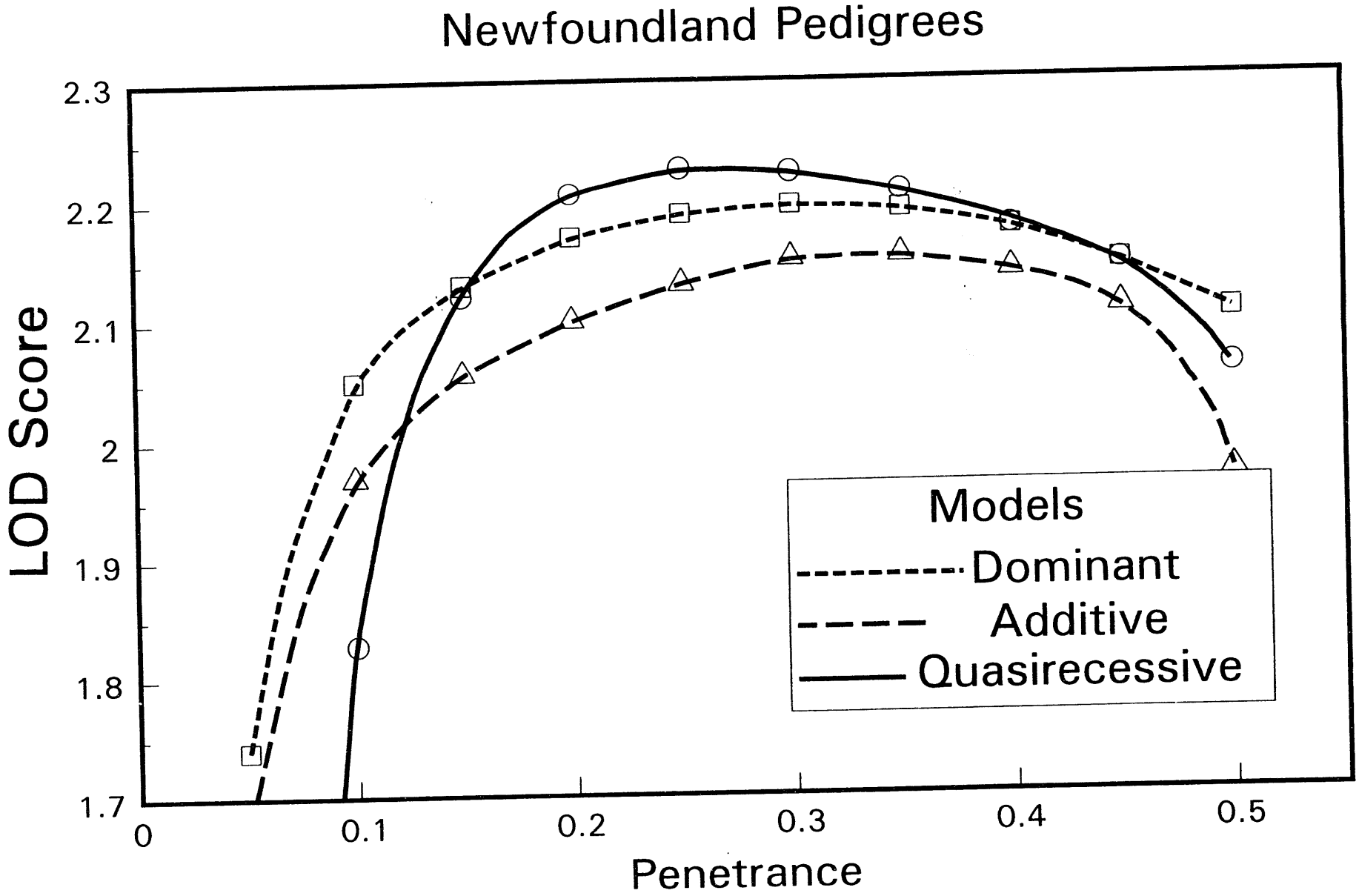
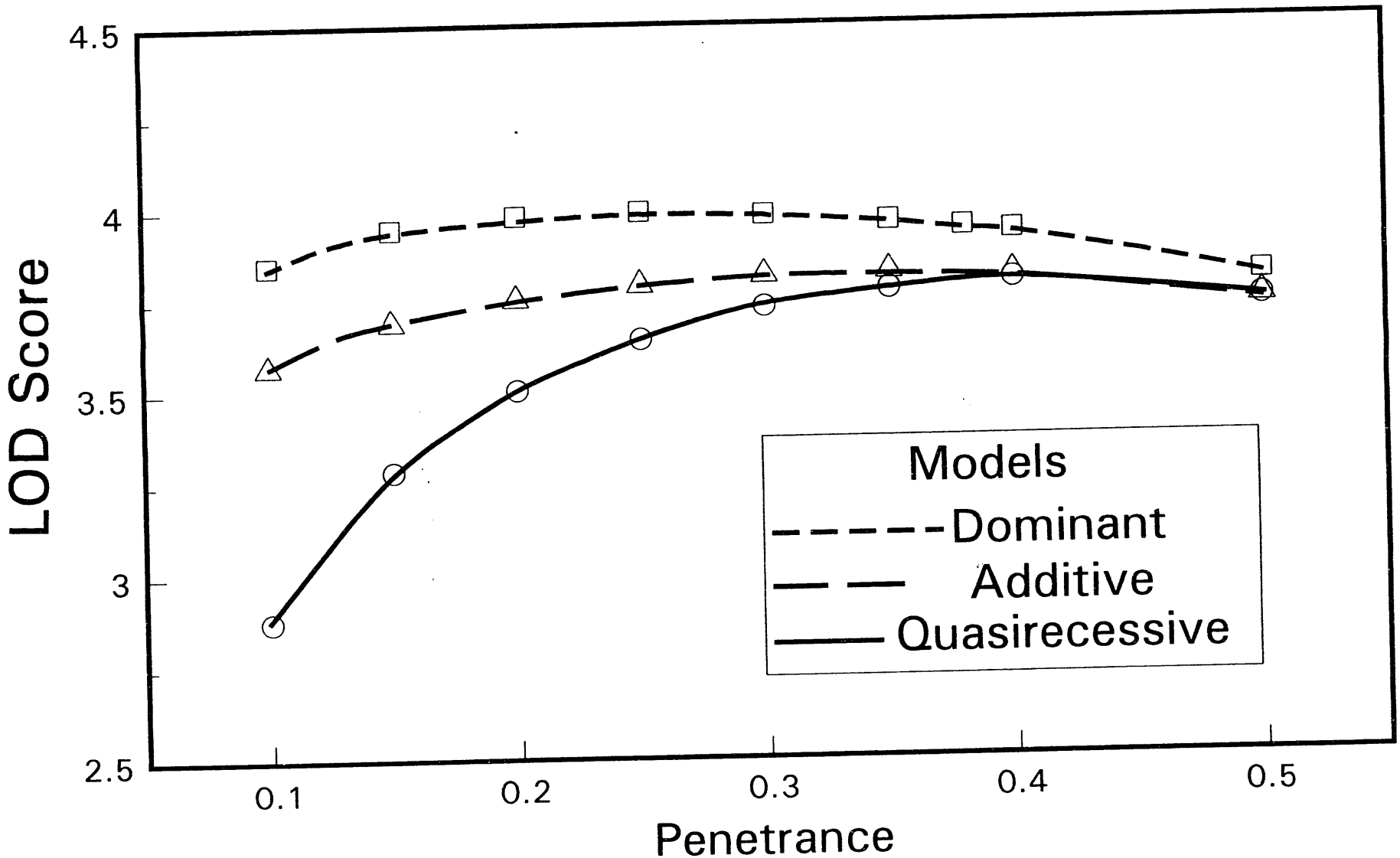


Figure 7: Penetrance versus Lod Score

With Allowance for B-27 Population Association



Francis L. Black, Ph.D.

INTERNATIONAL CONFERENCE ON IMMUNOGENETIC RISK ASSESSMENT
IN HUMAN DISEASE
CHARLESTON SC

No Specific Immunological Deficiency but Restricted Polymorphism of the Population as a Whole May Explain Susceptibility of New World People to Infectious Disease

Francis L. Black

7 March 1994

The indigenous populations of this country, of the Americas in general and, indeed, of all areas that had been isolated prior to the age of the European explorers, suffered terribly from infectious disease after contact. It is not possible to define the number who died, partly because no one counted, but also because the losses continued over centuries. Some populations were able to regenerate between major epidemics, only to be knocked down again. Many of the surviving populations are genetically mixed and we have inadequate data on what part of their gene pools actually derive from indigenous inhabitants. Many groups have been totally exterminated and a conservative estimate is that worldwide, at least 90% of the New World population has been lost (1). It is commonly assumed that New World people died because they were genetically incapable of mounting an adequate defense against the onslaught of diseases that were new to them. This, can be reduced to imply that their immune systems are in some way inadequate. If indeed the New World people have serious lacunae, determination of these gaps should tell us something of the evolution of the immune system and failure to find them should send us searching elsewhere for the reason for the high New World mortality. I will show that they can, in fact, mount very effective immune responses, but that the homogeniety of each population may be the root of the problem.

Study Population

In order to search for immunological lacunae one would like to have a population that has not been pre-selected. The original New World populations may, or may not, have included some persons with fully competent immune systems whose progeny would have been favored by selection. A search for unselected populations is most nearly met in South American rain forest. The people of the central Amazon basin, who were accessible by canoe, were quickly co-opted into a common, racially mixed society. However, above the fall line, around the periphery of the basin, many groups persisted, without regular contact, maintaining their isolation assiduously, until well into the present century. One cannot be sure they do not include refugees from the initial onslaught of disease and slave raids, but selection for resistance to new diseases has been minimal. Their unselected state is made manifest by the bitter fact that, when they are contacted, they regularly suffer serious depopulation (2). I will refer to these groups as "Tribes" because they have distinctive languages and customs.

Each tribe forms a distinct genetic and epidemiological unit. All presumably come from a common stock but this commonality occurred about 20.000 years ago. They separated into diverse languages long before Indo-Europeans diversified in Europe. Intermarriage between tribes occurs rarely. Only 0.7% of current

marriages studied by Salzano and Callegari-Jacques were inter-tribal (3). Infections have been transmitted directly from one tribe to another, but more often transmission has been via the larger society. We, (SLIDE) working over a period of 20 years, have studied genetics and immune responses in more than 20 tribes. Some of antigenic agents we introduced deliberately as vaccines, some occurred naturally.

Pneumococcal Polysaccharide Responses.

As one test of the adequacy of the immune systems we studied antibody responses to twelve of the polysaccharides of the Pneumococcal vaccine in seven tribes. On a continuing basis, pneumonia is the greatest single cause of death in these populations. Specific identification of the causative agent is seldom possible, but data from New Guinea indicate that, there at least, it is various types of Streptococcus pneumoniae (4). This system is also attractive for study because antibody to epitopes repeated in the polysaccharide is the dominant element in immunological defense. Gerry Schiffman measured pre- and post-vaccination antibodies in 381 persons. Jay determined Gm and Km allotypes in 371 of these, and we determined the three class I HLA antigens in 306.

Rather to our surprize, prevaccination antibody levels were high in the Amerinds, relative a U.S. sample. Initial levels in the Amerinds were higher for all 12 types and six-fold higher overall. In spite of these high initial levels, responses in the Amerinds were generally better than in the U.S., and similar to those seen in New Guinea (Table 1). It is possible that the pre antibodies were generated in response to polysaccharides from other sources and they may not mean that all the tested Streptococcal types had passed through every village. The strong responses may have been due to this priming rather than constituent. To determine the effectiveness of the immune systems in responding to pneumococci, it was necessary to look more closely at associations with specific immunogenetic traits.

We chose to emphasize the increase in antibody rather than the final level, or some value corrected for sensitization. To normalize the distribution of changes that followed vaccination, the root of the antibody rise was used for 9 of the 12 types. The mean level of response was found to vary from one tribe to another. Genetic differences may play a role in this, but each tribe has a distinctive history of exposure that may have played a key role. To make the data comparable across tribes we used deviation from the tribal mean. No pattern of difference dependent on age or sex was found and no adjustment made for this. The mean deviation for each type is 0 and significant genetic associations are evaluated by difference from this baseline. Responses to the 12 types were not independent of one another but strongly correlated.

Km The immunoglobulin allotypes seemed a good place to look for defects in as much as Granoff et al have reported that the response to Haemophilis influenzae b polysaccharide is dependent on both Km and Gm (4). Such defects may be T cell independent and thus dependent on simpler mechanisms than other immune responses. All the tribes we have studied have both Km1 and 3, but allelic frequencies vary. In the present sample the mean Km1 frequency .430. Overall, there was no pattern of difference in response to the 12 polysaccharides that could be related to this polymorphism (Table 2). When individual pneumococcal types were examined, the response to type 19 in heterozygous persons is elevated enough to come close to

a P of .05 but this is the only one of 36 values that individually approaches significance.

Gm Demographically, the distribution of Gm is more distinctive than Km. Two similar haplotypes, 1,17,21 and 1,2,17,21 make up more than 98% of the repertoire. Several members of one tribe, not tested for pneumococcal response, have an excision or defect in the 2l sequence from the 1,2,17,21 haplotype. Six of 20 tribes have a low prevalence of 3,5,13 for an overall frequency of this haplotype of .017. Other haplotypes are rare and diverse and probably represent admixture with Caucasians or Negroids. Granoff has reported that, what may be the same 3,5,13 haplotype as we found, when paired with in the haplotype 1,17,21 and in association with HLA B5, is associated with reduced risk of epiglottitis in H influenzae infection. Only 19 persons in the vaccinated sample had this haplotype, and their pneumococcal responses did not differ significantly from the mean either when considered all together (Table 3) or when in association with 1,17,21 or B5. The number was inadequate to examine the dual association.

As for the main Gm dichotomy, persons with the 1,17,21 haplotype made more pneumococcal antibody than persons with 1,2,17,21, but neither set differed from the combined mean. With this borderline exception, there is nothing here to suggest a deficient pneumococcal response, but please note the greatly restricted Gm polymorphism.

HLA We have also looked for an association between HLA Class I haplotype and response to the pneumococcal vaccines. At the class I loci the South Amerinds have only types 2, 24, 28 and 31 at A; 35, 39, 48. 51, 53, 60 and 62 at B and at the C, w1, w3, w4, w7 and probably a single blank allele. The blank usually appears in the same haplotype. This contrasts with 19 to 40 A and B alleles and a much more diverse C Blank in the world's major populations. The B35/53 split in the Amerinds has only been identified serologically by B4/B6 associations and needs to be confirmed on a molecular basis. This and the B48/60 distinction were not made in all subjects included in the pneumococcal vaccine sample and these pairs have been lumped for the present analysis.

Not only is an unusually small number of alleles carried by this population, but they are concentrated in a few haplotypes. Of 100 haplotypes we might have distinguished, only 31 were found in the current sample and six account half the gene pool. This compares to about 9000 haplotypes distinguishable by comparable methods in major cosmopolitan populations.

No general association was found between haplotype and mean response to the polysaccharides (Table 4). The responses in persons with the haplotype A24,B51,CB1 were high with P <.05 but considering the number of haplotypes examined this carries no significance. Because the number of different haplotypes was small it was not unusual to encounter several people with the same Class I phenotype. For instance, the study population included 13 people with A2,24 B51,62 Cw3,B1. This is close to a one in a million occurrence in cosmopolitan communities. The variance in level of pneumococcal antibody response within these groups was only 63% of the variance between phenotypes, suggesting that MHC phenotype does play some role. There is nothing however, to indicate that any particular Amerindian phenotype is significantly inefficient. The explanation of frequent failure to thrive could not be ascribed to

inefficient HLA genes.

Other Immune Responses.

I have emphasized immune response to pneumococcal polysaccharides because the data is relatively extensive and well controlled. It does not, however, test the whole immune response, because it may be T cell independent. We have also looked at many other systems. The response to viral vaccines would be strongly dependent on T helper cells. Responses to measles, rubella, mumps, yellow fever, poliomyelitis and influenza as well as to tetanus toxoid have all been examined without revealing any deficiency. Much of this work has been published previously (6-8). I would emphasize now, for later reference, that with almost all vaccine systems a standard microbial preparation is administered to all recipients. The polio vaccine is the only one that spreads from person to person generating variants in the process. Even with this vaccine, however, all members of a village are usually vaccinated at one time and, in the situations we have studied, relatively few are infected by anything other than the standard strains.

Anti-hemagglutinin titers induced by the measles vaccine in virgin populations will serve to illustrate the strength of immune response seen in Amerindian populations. Overall, the titers observed in virgin soil Amerind populations are every bit as high as in experienced populations and higher than in a group of Icelanders who had not seen measles for at least a generation, but whose ancestors had been selected by it (Table 5). Again persons with the same haplotypes exhibit less variation in titer that the whole group, but it has been difficult to pin this down to significant differences associated with individual haplotypes (Table 6). Sometimes a haplotype is associated with high titer in one tribe and low in another (Table 7) suggesting that it is not the Class I alleles that are relevant, but some linked gene.

Delayed Sensitivity

We have also examined delayed sensitivity responses as one measure of cytolytic T cell function. In passive transfer experiments only 16 of 26 persons accepted ragweed sensitivity, a foreign antigen in this area. However, ascaris tests were universally positive and IgE levels were greatly elevated (mean = 10,550 mg/ml). Persons naturally immunized by candida and tuberculosis and well as by BCG have been tested and gave normal ranges of reaction. It seemed probable, therefore, that cytolytic cells failed to respond to passive transfer because they were precommitted by combination with the high levels of antibody to parasitic infections, and not because they were defective.

Non-Immunological

There is one disease to which the Amazonian Indians lack resistance commonly found in other people living in wet tropical climates and that is malaria. Three forms of malaria: falciparum, vivax and malariae, occur in the area. Malariae could be indigenous, because it persists in South American monkeys, but the two more virulent types are probably post-Columbian introductions. Unlike Africans the Amerinds do not carry hemoglobin S, do not have glucose-6-phosphatase deficiency, and do carry the Duffy antigen. Unlike South Asians they do not carry either type of thalassemia, or hemoglobin E and unlike lowland New Guineans, they do not have HLA A11. In fact they do not have any of the genetic traits associated with malaria resistance except perhaps HLA B53. As noted this requires confirmation by molecular analysis, but Class I genes undergo frequent

recombination in these populations (9,10) and the populations carry the components of the B53 allele in B35 and B4 in association with B51. The Amerinds lack resistance to malaria relative to other tropical people, but they are no worse than most European Caucasians, who have managed to survive in the area.

Synthesis

It is patently impossible to prove the negative, that South Amerinds do not have any serious immunological deficiency. However, the deficiencies we have been able to find have been very spotty and of limited significance. It may be frustration, but I am inclined to believe that specific deficiencies cannot adequately explain the poor survival of New World people in the face of a "world class" spectrum of infectious disease. Some other explanation must be sought. The one characteristic does appear consistently and emphatically in these studies is a low level of polymorphism at various immunological loci. Restricted diversity similar to that which we found in the Amerinds, has been observed in all New World races whether they passed through a geographic bottleneck like the Amerinds or not like the Khoi-San of Southern Africa.

There have been many efforts at explaining the very high polymorphism that occurs in several MHC loci. It is evident that high levels of polymorphism reduce homozygosity, and where each allele confers the ability to respond to a limited spectrum of epitopes, heterozygosity could double the number of responses. This, advantage, however, comes partially balanced by a need to eliminate additional epitopes as self. Deviation from Hardy Weinberg has been observed directly in the Amerind population (11) and more generally as a balance between allele frequencies (12) and as an excess of functional over synonymous base changes (13). But the extent of this deviation is limited and it is inadequate to explain the phenomenon.

I suggest (14) that variability of the pathogens needs to be factored into the equation; that when pathogens adapt to avoid an immune response they become more virulent in other hosts who carry the same set of immunological genes; and that virulence of an organism can depend on the frequency with which it encounters serial hosts with a uniform immunological repertoire. By this mechanism, limited genetic diversity becomes the fatal chink in the immunological armor of New World people, wherever they live. The immunological problems of the South Amerinds do not derive from any specific deficit in the individuals so affected, but in the limited diversity of their population as a whole.

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COLLABORATORS IN THE STUDY OF IMMUNOGENETICS AND
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Roy Capper	Yale, New Haven	HLA typing
Yvonne Gabbay	Evandro Chagas Belem	HLA typing
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Jay Pandey	MUSC, Charleston	Allotypes
Sydney E.B.Santos	UFPa, Belem	Genetic Characterization
Joao Guerriero	UFPa, Belem	
Francisco Salzano	UFRGS Porto Alegre	
Walter Hierholzer	Yale, New Haven	Medical Evaluations
Richard Lee	Yale, New Haven	
Francisco Pinhiero	Evandro Chagas Belem	
Alexandre Linhares	Evandro Chagas Belem	

Essentially every member of each tribe willingly gave time, endured repeated needle sticks and, occasionally, suffered significant vaccine reaction.

Table 1. Response to pneumococcal Polysaccharide Vaccine
Mean Antibody Increase in Nanograms

	USA	South Amerinds	Papua New Guinea
No. Tested	20	381	20
Type 1	285	253	1800
3	589	1750	900
4	228	1274	2900
6A	154	502	1800
7	32	1109	700
8	199	2987	1200
9	188	798	-
12	114	817	700
14	87	848	3300
18	620	1386	6100
19F	36	436	-
23	1603	997	2800

Table 2. Response to Pneumococcal Polysaccharides, Relative to Tribal Mean, In relation to Km
(Km3 was not determined in all tribes. Specimens in which Km1,1 and Km1,3 could not be distinguished are omitted.)

Type	N		1	3	4	6A	7	8	9	12	14	18	19F	23
Km1,1	40	x	.184	-.022	.066	.219	.053	.059	.235	-.475	.099	.052	.272	.037
		t	.499	.182	.270	1.217	.454	.647	1.868	1.589	.717	.448	1.777	.375
Km1,3	166	x	-.067	-.007	.012	.008	.058	-.022	-.106	.068	.121	-.020	.196	.019
		t	.335	.137	.149	.121	.911	.556	1.835	.572	1.341	.305	2.786	.351
Km3,3	115	x	.229	.089	.016	-.085	-.023	.033	.114	.170	.017	.020	.036	-.031
		t	1.087	1.373	.109	1.020	.327	.739	1.158	.949	.249	.243	.555	.496

Table 3. Response to Pneumococcal Polysaccharides Relative to Tribal Means, In relation to Gm

	N	Mean Response 12 Types	s.e.
Gm2+	194	-.043	.027
Gm2-	177	+.066	.041
Gm5,13+	19	-.088	.067

Table 4. Response to Pneumococcal Polysaccharide Relative to Tribal Means by HLA A,B,C Haplotypes. Only Haplotypes with >7 Persons Shown.

B C Alleles		35,w3	35,w4	39,w7	51,w3	51,B1	60,w3	60,w4	62,w1	62,w3
A Allele										
2	N	13	22	9	11	80	24			31
	x	-.098	-.029	-.309	.009	.016	-.088			.025
	t	.69	.37	2.53	.05	.11	.81			.27
24	N	26	27	11		8	18	8		62
	x	-.117	-.061	.099		.397	.072	.338		-.065
	t	1.46	.81	.55		3.18	.61	2.39		1.05
28	N		14	19			19			11
	x		.191	.009			.032			.440
	t		1.09	.07			.36			2.70
31	N	26	48	15				9	9	38
	x	-.053	.068	.048				-.048	.051	.181
	t	.91	1.05	.34				.21	.26	1.76

Table 5. Measles Antihemagglutinin Titers 4 Weeks After Receiving Schwartz Vaccine

	N	Mean Log, Titer
Mixed Race Brazilian	146	8.88
Iceland	179	6.25
South Amerind	82	9.08

Table 6. Sources of Variance in Measles Anti-Hemagglutinin Titers

Source	DF	SS	F	P
Age	1	7.09	3.73	.054
Age^2	1	15.04	7.93	.0053
Haplotype	124	327.74	1.39	.016
Tribe	7	68.47	5.15	.0001

Table 7. Measles Anti-Hemagglutinin Titers in Persons with Same Class I Haplotype in Two tribes

	Parakana		Waiapi	
	N	Mean Log Titer	N	Mean Log Titer
28,60,w3	24	7.23	32	9.31
Other	96	7.75	200	8.69
P		.07		.02

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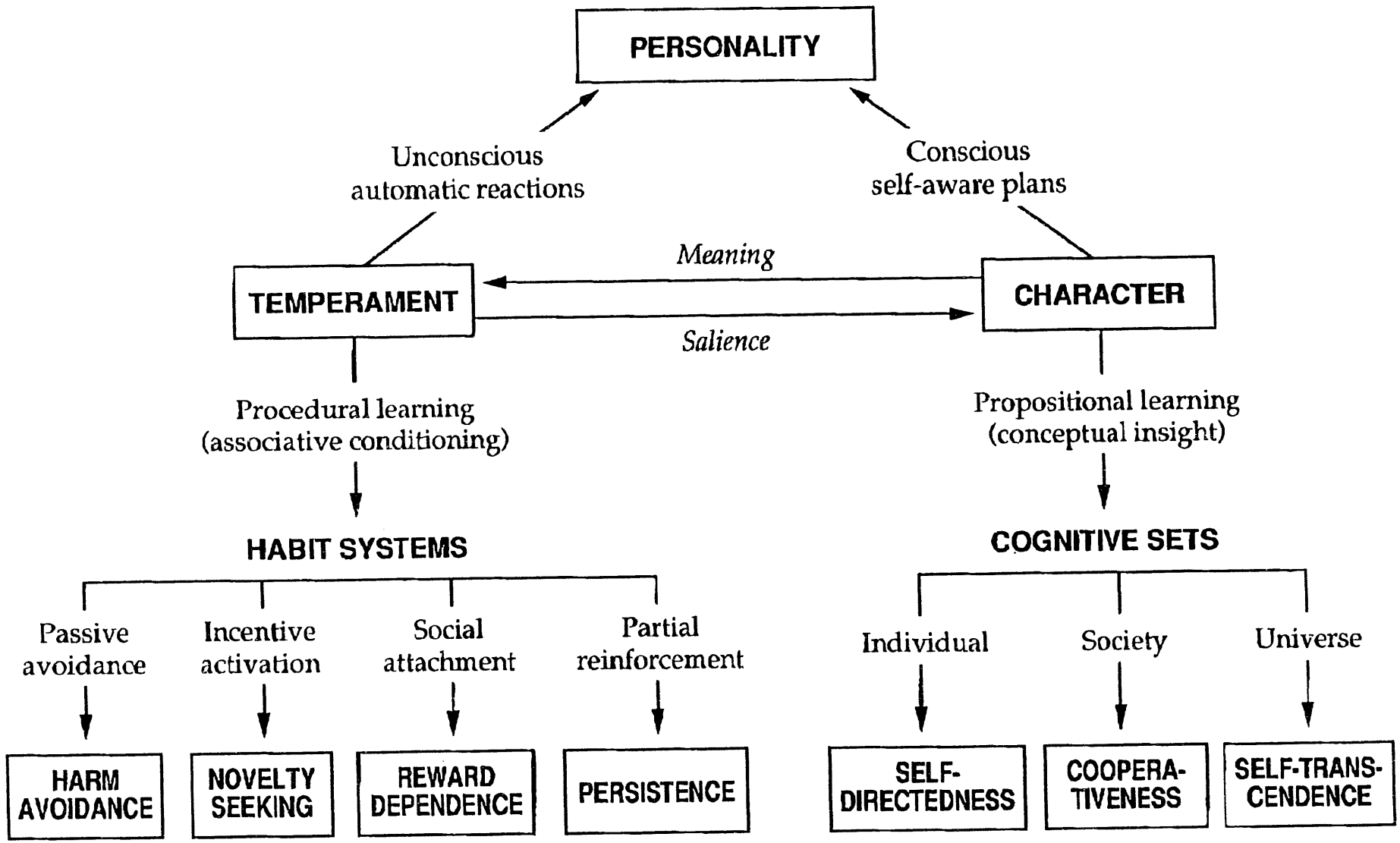
PERSONALITY
Unconscious
automatic reactions
Conscious
self-aware plans
Meaning
TEMPERAMENT
CHARACTER
Salience
Procedural learning
(associative conditioning)
Propositional learning
(conceptual insight)
HABIT SYSTEMS
COGNITIVE SETS
Passive
avoidance
Incentive
activation
Social
attachment
Partial
reinforcement
Individual
Society
Universe
HARM
AVOIDANCE
NOVELTY
SEEKING
REWARD
DEPENDENCE
PERSISTENCE
SELF-
DIRECTEDNESS
COOPERA-
TIVENESS
SELF-TRANS-
CENDENCE

Table 1.3. Brief Descriptors of Extreme Variants on the Seven Dimensions of the General Biosocial Model

Personality Dimension	Characteristic Descriptions	
	High Scorers	Low Scorers
TEMPERAMENT		
Harm Avoidance	Fearful Worried	Bold Confident
Novelty Seeking	Quick-tempered Excitable	Slow-tempered Stoical
Reward Dependence	Loving Sentimental	Cold Practical
Persistence	Perseverant Overachieving	Unambitious Underachieving
CHARACTER		
Self-Directedness	Responsible Resourceful	Immature Ineffective
Cooperativeness	Empathic Compassionate	Self-absorbed Revengeful
Self-Transcendence	Spiritual Selfless	Materialistic Proud

Table 5.13 Estimated causes of resemblance in Seven independent factors of ersonality from the California Personality Inventory (Loehlin, 1982)

Personality Factor	Genetic Heritability	Common Environment
TEMPERAMENT		
Extraversion	67	- 3
Neuroticism	46	9
Persistence	46	- 8
Intellectual curiosity	45	6
CHARACTER		
Masculinity-femininity	10	35
Intolerance of ambiguity	24	25
Cynical-tolerant	33	12

Parameters were estimated for r(MZ) = H + C, and r(DZ) = .5 H + C where H is additive genetic heritability (that is, H = A and D = 0), and C is common family enviroment.

Table 5.18. Multiple kinship correlations (x100) about personality traits rated by performance measures from the Objective-Analytic Test Battery in 12 to 18 year old boys in Illinois and Ohio (Cattell et al, 1957, 1981a,b, 1982b)

Personality Traits		Kinship Correlations				Causal Components		
Descriptors*	Factor #	MZT	DZT	ST	UT	H	C_T	C_S
COOPERATIVE	(I)	59	58	35	20	16	57	27
Group conformity	20+							
(1957)		52	58	31	-19			
Deferential	28+							
(1982)		84	60	38	36			
(1957)		35	47	26	34			
SELF-WILLED	(II)	53	60	36	13	16	67	28
Assertive	16+							
(1981)		62	64	34	7			
(1957)		24	21	33	40			
Independent	19+							
(1981)		68	60	38	9			
(1957)		50	75	41	0			
SELF-FORGETFUL	(VI)	47	59	13	29	-28	71	27
not self-seeking	26-							
(1982)		71	68	7	37			
(1957)		15	11	42	17			
CHARACTER - mean						1	65	27
EXTRAVERTED	(III)	61	39	24	22	24	17	12
Exuberance	21+							
(1981)		57	37	23	14			
(1957)		85	57	38	23			
Extraversion	32+							
(1981)		47	37	23	29			
RESPONSIVE	(IV)	59	24	25	23	37	6	6
Warm-hearted	22-							
(1957)		59	24	25	23			
CONSCIENTIOUS	(V)	56	31	17	19	23	6	6
Control	17+							
(1981)		28	-4	-13	6			
(1957)		55	40	36	20			
Mobilized energy	23+							
(1982)		84	66	42	38			
(1957)		55	19	17	11			
NEUROTIC	(VII)	77	47	26	11	45	17	4
Anxiety	24+							
(1982)		77	47	26	11			
TEMPERAMENT - mean						32	12	7

*Descriptions of the seven second-order factors consistently obtained from factor analysis of the objective test battery are capitalized and in bold

Robert C. Elston, Ph.D.

Abstract

Genetic markers that are sufficiently polymorphic (as measured by their heterozygosities) can be used in linkage and association analyses to detect Mendelian segregation underlying disease phenotypes. Each type of analysis can either be based on a specific genetic model or not make any assumptions about the mode of inheritance of the disease. Principles underlying these methods are reviewed, and the assumptions underlying them stressed. Association analyses are more powerful, provided there is linkage disequilibrium between the marker and disease loci; however, only linkage analyses have power in the absence of such disequilibrium. For this reason models that allow for both kinds of tests are preferred, and such models must adequately approximate the complexity of the disease being studied.

DRAFT

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Linkage and Association to Genetic Markers

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Introduction

There are two major approaches that can be used to identify genes that underlie a human disease. The first is the "linkage" approach, in which we study a set of polymorphic loci that we have no reason to believe are functionally related to the disease, but may nevertheless exhibit familial cosegregation with alleles predisposing to it. The second is the "association" approach, which presupposes we have prior information suggesting that the disease under study is caused by allelic variation at a particular candidate gene locus. In each case the genetic loci studied are "markers," in that they mark either the disease genes themselves or their approximate positions on the chromosomes. To be useful for this purpose, the mode of inheritance of a marker must be well understood and the marker must be polymorphic. Usually, the different phenotypes of a marker will be determined by segregation at a single locus, but this is not essential. By "polymorphic," we mean that the most common phenotypic form occurs in less than a certain fraction of the population. In the case of a marker determined by a series of multiple alleles, for example, polymorphic can be defined to mean that the relative frequency of the most prevalent allele is no larger than 0.99.

This paper focuses on the biometrical methods of analysis used, linkage and association analysis, once we have collected disease and marker data on a sample of persons. *Linkage* is a well defined genetic relationship between two loci: two loci are said to be linked if they are on the same chromosome and close enough that their alleles do not assort independently at the time of gamete formation. We shall be concerned with linkage between

marker and disease loci, i.e. between a locus at which allelic variation underlies marker phenotypes and a locus at which allelic variation is associated with the disease under study. The phenotypes associated with linked loci typically show no association in the population, but, as will be explained later, the atypical situation is becoming of more and more interest. The use of linkage analysis to uncover disease loci has unfortunately been called the "reverse genetics" approach. This misnomer arises from a misconceived belief that a straightforward genetic approach should start by studying DNA and its immediate products, completely ignoring the fact that genetics has to do with the study of genes and *gene*rations. The search for linkage has also been called a "shotgun" strategy, because for a long time only relatively few markers were available, scattered at random throughout the genome. I prefer to talk of a "global search" strategy, because it is now both possible and feasible to use linkage to search the whole human genome for disease genes (Elston, 1992).

A marker and disease are *associated* if their phenotypes are not independently distributed in the population. In the seventies, many diseases were shown to be significantly associated with one or another HLA allele. With forty or so HLA alleles investigated in a study, there is about 90% probability that at least one will show significant association at the 5% level with a disease that is not associated with it. It is common practice now to allow for multiple tests when quoting significance levels in association studies. It should be recognized that the significance of any one test is not changed just because other tests have been conducted, but an adjustment for multiple tests is appropriate if a particular result is singled out simply because it is the most significant of a set of tests. Much more difficult, however,

is the problem of how to interpret a single significant result when a candidate gene has been studied for association with a disease. The scientific interpretation of a significant result depends on the relative strengths of prior evidence for or against the alternative hypotheses (Browner and Newman, 1987). What is of interest is the probability, given the significant result, that there is in fact an association. The significance level, or probability of the *result found* given there is *no* association, can only be converted to this probability of interest if we can assign prior probabilities to the competing hypotheses of association and no association. In both linkage and association analysis we have the problem of quantifying our prior beliefs that there is a genetic locus underlying the disease etiology. But whereas, given that such a locus exists, we can use genetic knowledge to quantify the prior probability that it is linked to a particular marker or set of markers (clearly, it must be linked *somewhere* on the genome), there is no analogous quantitative theory that can be used for an association study. Unless it has impeccable credentials, a candidate gene's election can be risky business!

In this paper I give an overview of methods used in both linkage analysis and association analysis. In each case the methods may or may not be based on a genetic model and I call these methods model-based and model-free, respectively Every statistical test must, of course, be based on a probability model. I use the terms model-based and model-free to distinguish between the methods that do and do not make specific assumptions about the mode of inheritance of the disease under study. In the case of association, it will be especially important to consider what might be its cause, as only by doing so is it possible to develop a detailed model-based method of analysis. We shall then see that the distinction

between disease linkage and association, at least to genetic markers, is more apparent than real. I start with a brief discussion of how to quantify the polymorphism of a marker.

Quantifying Polymorphism

Botstein et al. (1980) defined the polymorphic information content (PIC) of a marker for studying linkage to a rare dominant disease. What is needed, however, is a measure that is independent of the mode of inheritance of the disease being studied, which is often unknown, and also preferably independent of whether a linkage or an association study is to be conducted. Assuming, as is the case with most DNA markers, that all the alleles are codominant, the heterozygosity, or proportion of the population that is heterozygous, is a simple measure of a monogenic marker's usefulness. This can be estimated from a sample in the usual way, as the sample proportion of heterozygotes. Usually the genotypic frequencies of a marker will be in Hardy Weinberg equilibrium, so that the heterozygosity is estimated more precisely as

$$1 - \sum_i p_i^2 \qquad (1)$$

or unbiasedly as

$$1 - (2n \sum_i p_i^2 - 1)/(2n - 1) \qquad (2)$$

where p_i is the estimated (relative) frequency of the i-th allele, i.e. $r_i/2n$, where there are r_i copies of the i-th allele in a random sample of 2n alleles (n persons).

Because heterozygosity is often estimated on the basis of a relatively small sample, it is important to calculate the standard error of such an estimate. The sampling variance of the heterozygosity estimate (1) based on a random sample was shown by Nei and Roychoudhury (1973), assuming codominance of all alleles, to be

$$\frac{(2n-1)}{4n^3}\{(3-4n)\ (\sum_i p_i^2)^2 + 4\,(n-1)\ \sum_i p_i^3 + \sum_i p_i^2\}\ ,$$

and this should be multiplied by $4n^2(2n-1)^2$ for the unbiased estimate (2). In this formula p_i is the true allele frequency, but in practice the estimate is used in its place.

Model-free linkage analysis

Let D be the allele at a disease-predisposing locus, and M the allele at a marker locus, that a family member has inherited from one parent; and let $\bar{D}$ and $\bar{M}$ be the alleles at the same loci, respectively, inherited from the other parent. Then the recombination fraction between the two loci, θ, is defined as the proportion of gametes transmitted in which a recombination has occurred, i.e. gametes that are $D\bar{M}$ or $\bar{D}M$. We are not concerned in this definition with whether or not D and $\bar{D}$, or M and $\bar{M}$, are recognizably different, only the fact that their parental origins are specified. The recombination fraction between two loci may depend on sex, race, age or some other characteristic of the family member, but I shall

assume for simplicity of exposition that it is the same for all members of the population. For two unlinked loci, $\theta = \frac{1}{2}$; for two linked loci, $\theta < \frac{1}{2}$.

Because the genetic mechanism underlying a disease trait is often unknown, there is interest in methods of detecting linkage that do not require a knowledge of this mechanism. These methods make no attempt to estimate the recombination fraction θ, but rather are aimed at detecting the existence of disease locus by the fact that it is linked to a marker locus, i.e. $\theta < \frac{1}{2}$. The best known of these methods were originally developed for samples comprising sib pairs (Penrose, 1935; Haseman and Elston, 1972), but they can also utilize data on other pairs of relatives. They are all based on the fact that two relatives share a variable number of alleles identical by descent at a marker locus. Such alleles are direct copies of the same allele, as opposed to alleles that are the same but derived from unrelated persons (alleles identical by state). The number of alleles shared identical by descent by a pair of relatives can be either directly counted or estimated on the basis of marker phenotypes. At the very worst, we can use the number of alleles identical by state as an estimate; this becomes a close approximation to the number of alleles identical by descent as the heterozygosity of the marker increases. Two unilineal relatives share either one or zero alleles, while bilineal relatives such as sibs share zero, one or two alleles identical by descent at a marker locus. Unless there is a linkage between loci underlying the marker and the disease, there is no reason why a measure of the number of marker alleles shared should correlate with the relatives' similarity with respect to the disease trait.

Haseman and Elston (1972) showed that if a quantitative trait is determined in part by additive genetic variation at a locus linked to a marker, then, letting Y be the squared sib pair difference in the trait, π the proportion of alleles shared by the sib pairs at the marker locus, and θ the recombination fraction between the two loci, the regression of Y on π is $-2(1-2\theta)^2\sigma_a^2$, where σ_a^2 is the additive genetic variance due to the trait locus. It is not necessary to assume that this is the only locus that affects the trait, but the derivation does assume that the genotypes of the two loci, trait and marker, are independently distributed in the population. Because this regression coefficient is 0 if either $\theta = ½$ or $\sigma_a^2 = 0$, and negative only if $\theta \neq ½$ and $\sigma_a^2 > 0$, Haseman and Elston suggested the usual t-test for a regression coefficient as a test for the presence of a locus, affecting the trait, linked to the marker: a significantly negative value of t, based on a one-sided test, would be indicative of linkage. They also showed that it is not necessary to eliminate pairs for which π is not known with certainty, indicating how it can be estimated either from the sib-pair marker data alone, or from the sib-pair and parental marker data, if the marker allele frequencies are known. Amos (1988) extended the method to use the marker data available on all members of a nuclear family to estimate π for a pair of sibs, and the method was later extended to use all the marker information available on members of a pedigree to estimate π for both sibs and other pairs of relatives (Amos et al., 1990). If the trait is a dichotomous disease phenotype, then we can quantify "affected" and "unaffected" by two distinct numerical values and the test becomes identical to the t-test for testing whether the mean value of π is larger for concordant than for discordant sib pairs (Elston et al., 1973). In the absence of linkage, there is no reason why the mean proportion of alleles shared identical by descent should be different for

concordant and discordant pairs; in the presence of linkage, one would expect the proportion to be larger for concordant pairs.

It was shown by Hodge (1984) that the values of π for the different pairs of sibs in a sibship of more than two members are pairwise independent, a fact that underlies the validity of the t-test, found by Blackwelder and Elston (1982) using simulation studies, if all possible distinct pairs that can be formed from a sibship are assumed to be independent when performing the t-test. The regression coefficient for pairs of half-sibs is exactly the same as that for full sibs, a fact that makes it relatively easy to pool full-sib and half-sib data in an efficient manner to test for linkage (Schaid et al., 1994). The coefficients are different for grandparent-grandchild pairs, avuncular pairs and first cousin pairs (Amos and Elston, 1989), but in each case linkage results in a negative regression coefficient and lack of linkage (i.e. $\theta = \frac{1}{2}$ or $\sigma_a^2 = 0$) results in a regression coefficient of 0. Olson and Wijsman (1993) have indicated a method of pooling the information from different pairs of relatives in the same family to detect linkage in this model-free manner. Because the method used is that of general estimating equations, based on asymptotic considerations, a large number of families is necessary for their method.

Most of the information for linkage in these tests comes from the pairs of relatives that are concordantly affected, and so the study of affected pairs of relatives is considered to be an efficient design. In this case the sample mean of π (or its estimate) can be compared with its expected value for a random sample of relative pairs from the population – e.g. ½ for

sib pairs, and ¼ for grandparent-grandchild pairs; if there is linkage the sample mean will be increased. Similarly we can test for an increase in similarity at the marker locus among several affected members of a pedigree (Weeks and Lange, 1988). It should be noted that these methods essentially do not use a control group (discordant pairs of relatives), and so are more sensitive to any assumptions made about marker allele frequencies.

Model-based linkage analysis

The statistical significance of a model-based linkage study is commonly summarized by the maximum value of a lod score, which is often misinterpreted as the logarithm of the odds for linkage. The lod scores quoted in linkage analysis are *backward* lods, which are logarithms of likelihood ratios (Barnard, 1949). As such they measure the relative probabilities of observing a particular set of family data under very specific alternative hypotheses, one of which is usually a hypothesis of no linkage between two loci, i.e. $\theta = \frac{1}{2}$. The family data are the phenotypes associated with the marker(s) and the disease, observed on the members of one or more families. A family may consist of as few as two, or as many as hundreds of, persons.

In order to calculate the likelihood for a set of family data we must have a completely specified probability model. In general, this requires knowledge of: (1) the inheritance mechanism underlying the bivariate phenotype (marker and disease), i.e. the number of loci involved and the number of alleles at each locus, (2) the population distribution of the

genotypes involved, i.e. the joint genotypic frequencies for both marker and disease loci, (3) the probability distributions of the phenotypes conditional on each genotype, often called the penetrance functions, (4) the distribution of offspring genotypes conditional on their parents' genotypes, and (5) the manner in which the families were sampled from the population. (Whereas in many statistical investigations we can reasonably assume we have a random sample from a certain population, so that the likelihood function has the same form as the underlying probability function, this is rarely the case in a linkage study of a disease). Details of how the likelihood is formulated, together with the many assumptions often made in calculating it, are discussed by Elston and Stewart (1971), Elston and Rao (1978) and Ott (1991). Unless the likelihood accurately reflects each of the various components, one should hardly be surprised if the resulting likelihoods have little relevance to the study being conducted. What is quite remarkable is the plethora of papers that have been published over the past decade whose main or sole purpose has been to point out that likelihoods based on incorrect probability models can lead to incorrect conclusions.

It is often assumed that a single recombination fraction θ is the only unknown parameter in the likelihood, so that for a given set of data the likelihood is written $L(\theta)$. This assumes that only two loci are involved, one for the marker and one for the trait; the population genotypic frequencies are known; the penetrance functions are known; and that θ is the only unknown parameter in the distribution of offspring genotypes conditional on their parents' genotypes. It so happens in this situation that the likelihood ratio $L(\theta)/L(\frac{1}{2})$ is not affected if the pedigrees for study are selected because of containing members with specific

phenotypes, provided that the phenotypes of only one of the two traits, marker *or* disease, are the basis for this selection. Therefore, provided we are in this situation and we are solely interested in this particular likelihood ratio, $L(\theta)$ and $L(\frac{1}{2})$ can be calculated on the assumption that we have a sample of families that has been randomly drawn from the population. Then the lod score, as a function of θ alone, is defined as $Z(\theta) = \log_{10} [L(\theta)/L(\frac{1}{2})]$.

Under the assumed model, the maximum likelihood estimate of the recombination fraction, $\hat{\theta}$, is that value of θ that maximizes the lod score. Provided this estimate is not constrained to be between 0 and ½, likelihood theory tells us that $2 \log_e [L(\hat{\theta})/L(\frac{1}{2})] = 2 \log_e 10 \, Z(\theta)$ is asymptotically distributed as chi square with one degree of freedom under the null hypothesis $\theta=\frac{1}{2}$. It follows that rejecting the null hypothesis $\theta=\frac{1}{2}$ versus the alternative hypothesis $\theta < \frac{1}{2}$ when $Z(\hat{\theta}) \geq 3$, a commonly used criterion to determine linkage, corresponds to a significance level of about 10^{-4} asymptotically. Given what we know about the human genome, and hence the prior probability of linkage between two loci (Elston and Lange, 1975), use of this significance level corresponds to about a 5% *posterior* probability of type I error, i.e. probability of there being no linkage once this significance level is reached (Morton, 1955; Elston, 1993).

Suppose we know nothing about the underlying inheritance mechanisms, can we nevertheless interpret a large lod score as indicative of linkage? It should not come as a surprise that in general the answer to this question is "no." However, under certain

circumstances a large lod score that has been calculated assuming a wrong probability model can indicate "significant linkage." Provided that the marginal probability model for one of the two traits is correct, marker *or* disease, the likelihood ratio will not be inflated in large samples by an incorrect marginal probability model for the other trait, if in fact $\theta = ½$ (Williamson and Amos, 1990; Amos and Williamson, 1993). Two things should be carefully noted about this result, if it is used to suggest linkage between a marker and a disease whose mode of inheritance is unknown: (1) everything assumed about the marker (such as allele frequencies and probabilities of mistypings) must be correct – it is not in general sufficient simply to assume arbitrary marker allele frequencies or to allow for arbitrary probabilities of marker mistypings in the model; and (2) one should not expect any estimate of the recombination fraction to be consistent, i.e. to approach the true value as the sample size increases – the statistical significance is only a measure of how unlikely the data are if in fact $\theta = ½$.

It is sometimes possible to obtain a consistent estimate of θ, as well as of other disease parameters such as penetrances and allele frequencies, by maximizing the lod score over both θ and these other parameters. Denote the collection of other parameters ϕ, with the corresponding lod score function $\log_{10}[L(\theta,\phi)/L(½,\phi)]$. Then the values $\hat{\theta}$ and $\hat{\phi}$ that maximize this function are consistent estimators provided the following conditions hold (Elston, 1989; Clerget-Darpoux, 1993; Hodge and Elston, 1994):

(1) The assumed genetic mechanism underlying the disease trait (the number of loci and the number of alleles at each loci) is correct, so that there exists a set of parameters ϕ that makes the probability model for the disease correct.

(2) The assumed genetic mechanism and all parameters relevant to the marker are correct.

(3) There is no population association between the disease and the marker.

This last condition should be particularly noted. Although failure of this condition invalidates many of the likelihoods commonly used for linkage analysis, it is a prerequisite for a successful association analysis.

Model-free association analysis

The simplest and most efficient design to study the association between a disease and a marker locus, without any regard for the cause of that association, is the case-control design. Suppose we have two random samples, one of N_1 cases (with the disease) and one of N_2 controls (without the disease), and each person is classified as having a particular marker allele (M) or not ($\bar{M}$). (One can further classify those persons with the marker alleles as having either one or two copies of it, but for simplicity I do not consider this possibility here). Let A, B, C and D be the numbers falling in the resulting four cells of a 2 x 2 table, as shown in Table 1. Then the *odds ratio*

$$\frac{P(\text{disease} \mid M)}{P(\text{no disease} \mid M)} \cdot \frac{P(\text{no disease} \mid \overline{M})}{P(\text{disease} \mid \overline{M})} = \frac{P(M \mid \text{disease})}{P(M \mid \text{no disease})} \cdot \frac{P(\overline{M} \mid \text{no disease})}{P(\overline{M} \mid \text{disease})} \quad (3)$$

is consistently estimated by AD/BC. Significance of the deviation of this ratio from 1 can be tested by the usual chi square statistic with one degree of freedom or, for small samples, by Fisher's exact test. If the second column of Table 1 is obtained by studying a random sample from the population, rather than a sample of persons without the disease, then AD/BC is a consistent estimate of the more meaningful *relative risk*

$$\frac{P(\text{disease} \mid M)}{P(\text{disease} \mid \overline{M})}, \quad (4)$$

the significance of which can be tested in the same way.

It is well known that if the samples are heterogeneous with respect to another risk factor, any association that is found could be due solely to this heterogeneity. In particular, the samples may differ in their genetic make-up. For this reason a method has been proposed, known as the haplotype relative risk method, in which both M and $\overline{M}$ originate from the same person (Rubinstein et al., 1981; Falk and Rubinstein, 1987). This and related methods have recently been the subject of considerable investigation (Ott, 1989; Terwilliger and Ott, 1992; Spielman et al., 1993; Knapp et al., 1993) and I shall review their most important aspects. These methods all use marker data obtained from persons affected with the disease under study together with marker data from their parents, comparing the parental marker alleles transmitted to the affected person with those not so transmitted.

Consider a sample of n affected persons and their parents, all typed for a marker. As before, let the marker allele of interest be M, and pool all others as $\bar{M}$. Each parent can be classified into one of the four cells of a 2x2 table, as shown in Table 1, depending on whether that parent's transmitted and nontransmitted alleles are M or $\bar{M}$. Let the number of parents falling in each of these cells be a, b, c, and d, as shown in the table. (If the offspring and both parents are $M\bar{M}$, we cannot know which parent transmitted M and which transmitted $\bar{M}$. But we know that one parent transmitted M and not $\bar{M}$, and conversely the other transmitted $\bar{M}$ and not M, so that these two parents contribute one each to the numbers b and c in the table.) Now the four marginal totals of Table 2 can be reorganized into the 2x2 table shown in Table 3, and this bears a resemblance to Table 1. Analogous to (3) we define the odds ratio

$$\frac{P(\text{transmitted}|M)}{P(\text{not transmitted}|M)} \cdot \frac{P(\text{not transmitted}|\bar{M})}{P(\text{transmitted}|M)} = \frac{P(M|\text{transmitted})}{P(M|\text{not transmitted})} \cdot \frac{P(\bar{M}|\text{not transmitted})}{P(\bar{M}|\text{transmitted})}$$

which is consistently estimated by (a+b)(b+d)/(a+c)(c+d). Furthermore, if the nontransmitted alleles (second column of Table 3) could be considered as a random sample rather than as a sample of alleles belonging to unaffected controls, (a+b)(b+d)/(a+c)(c+d) could be considered a relative risk, analogous to (4), and so it has been called the haplotype relative risk.

Note that in Table 3 every parent has been entered twice, so it should not be assumed legitimate to calculate from its entries the usual chi square statistic with one degree of freedom to test the significance of this relative risk. It is easy to show that the estimated

haplotype relative risk is equal to 1, i.e. (a+b)(b+d) = (a+c)(c+d), if and only if b = c (assuming n > 0). Furthermore, testing whether the haplotype relative risk is different from 1 is the same as testing whether the number of transmitted alleles that are M (a+b in Table 2) is significantly different from the number of nontransmitted alleles that are M (a+c in Table 2). The appropriate statistical test for this is McNemar's test, for which the chi square statistic with 1 degree of freedom is $(b-c)^2/(b+c)$, or for small samples we base our test on the binomial distribution with parameters b+c and ½. Several points should be noted about this test. First, it does not assume independence of the transmitted and nontransmitted alleles, i.e. it does not assume lack of association in Table 2. Second, it utilizes only information from the $M\bar{M}$ (heterozygous) parents: MM and $\bar{M}\bar{M}$ parents contribute only to the numbers a and d in Table 2, and hence are not used in this test. Third, the test involves no control group. Should $M\bar{M}$ persons for any reason transmit more M gametes than $\bar{M}$ gametes, regardless of whether or not the offspring is affected with the disease, this will tend to create a haplotype relative risk larger than 1. To guard against this possibility, either the marker should be previously tested for Mendelian segregation, or a table analogous to Table 2 should also be derived for a random sample of offspring, so that the entries a and b from the two tables can be put together in a fourfold table to test for association in the usual way.

Model-based association analysis

I have already noted that significant association between a disease and a marker can be due to chance, heterogeneity with respect to a confounding risk factor, or non-Mendelian

marker segregation. There is one other possible cause of association: a tight linkage relationship between the loci involved. I include in this, as a special case, the situation in which the marker locus has a pleiotropic effect on the disease phenotype, i.e. it is itself involved in the etiology of the disease. At equilibrium under random mating the alleles of two linked loci are independently distributed in the population, provided that the recombination fraction is strictly positive. However, if the recombination fraction is small (of the order of 1% or less), the population may not have reached equilibrium, so that the alleles of the two linked loci not only cosegregate in families but are also associated in the population. (It should be noted that assortive mating for a disease cannot *per se* lead to an association or linkage to a marker). Therefore it is often assumed, as a model for association analysis, that the genetic mechanism underlying the disease is monogenic, with a disease-predisposing allele D in (possible) linkage disequilibrium with a marker allele M.

Let the allele frequencies of D and M be d and m, respectively, and define a disequilibrium parameter δ such that the population frequency of the haplotype DM is $dm + \delta$, i.e. δ is the excess of the haplotype frequency over what would be expected at equilibrium under random mating. The recombination fraction between the two loci is denoted θ as before; the special case $\theta = 0$ and $\delta > 0$ is that of the marker having a pleiotropic effect on the disease. Now assume that there is no selection or mutation of gametes, the alleles at each of the two loci are in Hardy-Weinberg equilibrium, and that there is random union of haplotypes. Under this genetic model, Knapp et al. (1993) derived the

joint distribution of transmitted and nontransmitted haplotypes among the parents of affected children and proved the following:

(1) the haplotype relative risk due to a marker allele is always at least as close to 1 as is the relative risk; the two risks are equal if $\theta = 0$, and the haplotype relative risk is 1 if $\theta = ½$.

(2) there is no tendency for the haplotype relative risk method to favor a false-positive association, compared with the case-control design.

Under the specific model that I have just described, the transmitted and nontransmitted alleles are independent if $\delta = 0$, so that the entries in Table 3 then derive from 4n independent alleles. Thus, provided this model is correct, we can test the null hypothesis $\delta = 0$ by performing the usual one degree of freedom chi square test for association on the entries of Table 3. If there is any doubt about the genetic mechanism underlying the disease, this model-based test for association should not be performed unless the entries in Table 2 clearly suggest no association between the transmitted and nontransmitted alleles.

Under this same model, MacNemar's test is a test of the null hypothesis $\delta(1-2\theta) = 0$, i.e. it can be considered either as a test of association (null hypothesis $\delta = 0$) provided $\theta \neq ½$, or as a test of linkage (null hypothesis $\theta = ½$) provided $\delta \neq 0$. For this reason Spielman et al. (1993) have called this a transmission/disequilibrium test. They go on to show that if we

classify $M\bar{M}$ parents of several affected offspring according to the number of M alleles they have transmitted to these offspring, a total goodness-of-fit chi square statistic can be partitioned into orthogonal components that test different specific hypotheses. Suppose, for example, we have $M\bar{M}$ parents of two affected offspring, so that the number of M alleles transmitted can be 0, 1 or 2. If there is no selection or mutation and there is no relevance of the fact that the offspring have a particular disease, these numbers of alleles will be transmitted with probabilities ¼, ½ and ¼, respectively. The chi square statistic with 2 degrees of freedom that tests goodness-of-fit to these proportions can be expressed as the sum of two chi squares, each with one degree of freedom. The first of these corresponds to MacNemar's statistic, i.e. it provides a "transmission/disequilibrium test." The second chi square statistic tests whether the mean proportion of marker alleles the offspring share identical by descent, π, is equal to ½; it is thus a model-free linkage test based on pairs of affected sibs. These two chi square tests both test the null hypothesis $\theta = ½$; but the first test statistic only has power when $\delta > 0$, and in that case it has much more power than the second test statistic.

This last example illustrates the fact when there is association due to linkage disequilibrium, the most powerful test is one that includes both θ and δ in the model. There is no reason one or more disequilibrium parameters should not be included in a model-based linkage analysis, just as there is no reason one or more linkage parameters should not be included in a model-based association analysis. Thus, in the situation that is of most interest to locate and identify genes underlying disease, i.e. tight linkage and hence possible linkage

disequilibrium, linkage and association should be considered as two aspects of the same overall analysis. Both aspects should be tested, because (1) disequilibrium, when it exists is much more easily detected, and (2) even in the case of no recombination, there can be perfect equilibrium between the alleles at two loci.

Conclusion

Model-based methods of testing for linkage and association are preferred because they are more powerful than model-free methods. They should therefore always be used when we know, or have good information about, the genetic mechanism underlying a disease. To the extent that parameters of the genetic mechanism are unknown, they should be appropriately estimated as part of the testing procedure. The model-based methods used may be robust against some of the assumptions underlying them, but this should never be taken for granted. There is always the possibility of selective forces acting strongly on loci tightly linked to the disease and marker loci being studied, leading to a hitchhiking effect (Langley, this conference). For estimates to be valid, and for our tests to be both valid and powerful, the models used must adequately approximate the complexity of the disease being investigated.

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Table 1

Distribution of persons having a marker allele (M) or not ($\bar{M}$) in a sample of N_1 cases and a sample of N_2 controls.

Marker	Cases	Controls	Total
M	A	B	A+B
$\bar{M}$	C	D	C+D
Total	N_1	N_2	N_1+N_2 = A+B+C+D

Table 2

Distribution of 2n parents according to the marker allele transmitted, and the marker allele not transmitted, to an affected offspring.

Transmitted allele	Nontransmitted allele		
	M	$\bar{M}$	Total
M	a	b	a+b
$\bar{M}$	c	d	c+d
	a+c	b+d	2n = a+b+c+d

Table 3

Reorganization of the marginal totals from Table 2 to form a table similar to Table 1.

Marker allele	Transmitted	Nontransmitted	Total
M	a+b	a+c	2a+b+c
$\bar{M}$	c+d	b+d	b+c+2d
Total	2n	2n	4n

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Recent advances concerning human immunoglobulin allotypes or rather Mendelian polymorphisms of the human Ig gene cluster.

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TABLE 1 There are 28 bona fide human Mendelian Ig allotypes, characterizing 6 loci. Five of these, Am, Em, G1m, G2m and G3m, are situated in chromosome 14 band q 32 and one, Km, is in chromosome 2 band p 12. All are defined at the protein level and are strictly distributed within their proper Ig class or IgG subclass. Many of them are precisely defined as to amino acid and codon substitutions (see Grubb 1994 for a recent review). As seen below gene technology methods have permitted the distinction of many more sites exhibiting Mendelian polymorphism within the human Ig gene clusters.

TABLE 2

Monoclonal antibodies permit more precise Ig allotyping

Anti-Rh-antibodies are classically used as detectors in Gm allotype research. Because of the need for anti-Rh in the profylaxis of hemolytic disease of the newborn, monoclonal anti-Rh's carrying one only (or a few) of the IgG allotypes occurring in Caucasians are now available (see Tippet & Moore 1990). Thanks mainly to work led by Gerda G. de Lange (1988) at the Red Cross Blood Transfusion Center in Amsterdam, monoclonal anti-Gm's of several specificities are also available.

These 2 types of monoclonal antibodies represent an important methodological advance in allotyping and should be taken advantage of whenever possible.

RFLP:s of the human Ig HC genes and their relation to Gm allotypes

Eleven investigations of these RFLP:s dating from 1983-1994 are summarized in table 1. As can be seen, the number of polymorphic sites has considerably increased. Many of them are in positions which do not carry codons for Gm, Am or Em allotypes. Thus several switch regions, the δ gene and pseudogene regions ($\psi\varepsilon$, $\psi\gamma$) and and also the Ig G3 hinge regions display RFLP, all shown to be heritable. There is linkage disequilibrium between Gm, Am and the new polymorphic sites in Ig HC except for the RFLP in the μ switch and α_1 gene region. The number of observed haplotypes combined with Gm markers exceeds 100. The precise relationship between these many new polymorphic sites has not been elucidated. It has been shown that the RFLP's described by Lefranc & Rabbitts (1984) and Balbin et al. (1994) exactly tally with the A2m and with the G3m b and g allotypes, respectively.

RFLP:s of the variable region of the human Ig H gene cluster

V-gene related allotypes in the rabbit have been known since the 1950s. In contrast, allotypes ascribable to the human V regions have not been established at the protein level. In 1984 Johnson et al. observed heritable polymorphic sites in the VII gene family of the heavy chain in man by RFLP analysis and these observation have been extended since then. Figure 1 gives a schematic physical map of the IgH genes. It also indicates the positions of the heritable RFLP:s in relation to the V gene families.

As can be seen, we can count 18 polymorphic sites in families I-V. The allelic relationships are not well established for several of the V region polymorphism. Linkage disequilibrium is weak or absent between these RFLPs, in striking contrast to the polymorphisms of the constant region of the IgH chain. Several polymorphic sites have been described also for the kappa and lambda V region genes.

Allotyping at the genomic level by PCR, Ig subclass-specific amplification and allele specific probes

As mentioned, the amino acid and codon substitutions correlating with allotypes are precisely known in several instances. For example, G1m(f) and G1m(z) differ by a single base substitution (AAA - AGA) at position 214. The prerequisites for determining several of these and several other allotypes at the genomic level are therefore at hand. The use of Ig-subclass specific amplification is usually advisable as a primary step, since base composition may correlate with allotype within one subclass but with isoallotype in another subclass. Fig 2 demonstrates $\underline{G1m}^{f}$ - $\underline{G1m}^{z}$ typing at the genomic level.

As seen, the single-base substitution is detectable by the technique. It is clear also that all z dots representing homozygozity had greater diameters than those from heterozygons persons. This type of technique has been worked out also for $\underline{G1m}^{a}$, $\underline{G3m}^{b}$ and $\underline{G3m}^{g}$, meaning that these allotypes can be determined without any resort to serological reagents.

Schematic physical map of the gene cluster and polymorphisms in the human Ig HC cluster

The precise position of several of the Gm sites are known. This holds also for the RFLPs in this region because the nucleotide sequences are exactly known for most of the Ig HC genes as is of course also the cutting specificity of the restriction enzymes used.

Figure 3

More than 20 heritable polymorphic sites have thus been shown in the so-called constant genes. Strong linkage disequilibrium is valid for the $\gamma 3 - \alpha 2$ stretch. The new data on the μ switch and RFLP:s indicate a hot spot for recombination between δ and $\gamma 3$.

The number of possible variants of haplotypes for the IgH "constant" region genes is mathematically more than 10^6 because more than 20 polymorphic sites are known. The linkage disequilibrium restricts the observed number of variants: It is evident, though, that on an evolutionary time scale many recombinations have taken place. The ethnic variation in Gm haplotypes is indeed striking. (Cfr Steinberg & Cook 1981, Matsumoto 1989, de Lange 1989)

Comparison of genetic polymorphisms in the Ig HC and V regions

The V - J stretch of the human Ig H genes comprises approximately 1100 kb and the number of known polymorphic heritable sites is about 15. The Ig HC stretch is approximately 300 kb, and exhibits more than 20 polymorphic Mendelian sites. This indicates, perhaps, that this type of polymorphism is more common in the

so-called constant part. It is clear already that linkage disequilibrium is strong in the better part of the C cluster but is hardly observed within the V region.

Human Ig G subclass levels are related to allotype

Already in 1967 Yount et al. showed that G3m(b+) individuals had a significantly higher concentration of Ig G3 than G3m(b-) individuals. These observations have been extended particularly by Morell et al. 1972, Sarvas et al. 1989, 1991, 1993 and Oxelius 1993. There is consensus that the following associations hold statistically

$G1m^{a(x)}$: high level of IgG1

$G1m^{f}$: low level of IgG1

$G2m^{n}$: high level of IgG2

$G2m^{-n}$: low level of IgG2

$G3m^{b}$: high level of IgG3

$G3m^{g}$: low level of IgG3

In the studies of Sarvas et al. (1991), the IgG3 levels were two- to threefold higher in $G3m^{b}$ homozygous persons than in the $G3m^{g}$ homozygotes. $G2m^{n}$ homozygotes had a mean IgG2 level of 4.5 g/L, the heterozygotes 3.7 g/L, and those without the n marker 2.9 g/L. According to Sarvas et al. (1991), the quantitative differences may be ascribed to varying efficiency of the switch regions of the respective alleles.

Immunoglobulin responses in bacterial infections and vaccinations are allotype related

In mice there are several examples of correlations between immune responses and Ig allotypes.

The specific antibody response in vaccination with bacterial antigens has been measured and related to Ig allotypic constellation in numerous investigations in humans (Wells et al., 1971; Mackay et al., 1975; Pandey et al., 1979; Ambrosini et al., 1985; 1986; Sarvas et al., 1989). Flagellin from Salmonella, polysaccharide from pneumococci, meningococci, streptococci group B, and Haemophilus influenzae have been the immunogens. It is clear that the antibody titers to the polysaccharides is related to G2m(n) allotype, being higher in G2m(n) homozygous persons than in the G2m(-n) individuals. In several of the studies, the antipolysaccharide response was less in Km(1) persons than in Km(-1). A good antibody response to the protein flagellin was related to allotype G1m(a)G3m(g). Antipolysaccharide antibodies are known to be preferentially of subclass IgG2. The result in the vaccination studies fits, and should be seen in context with the pecking order of the Gm alleles described in the previous section.

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GENERAL APPROACHES TO THE STUDY OF THE GENETICS OF AUTOIMMUNE DISEASES

- Descriptive population studies
- Case-control analyses of frequencies of specific genes and their products
- Family studies
- Sib-pair analyses
- Reverse genetic molecular approaches
- Phenotype-genotype correlations after subsetting AID populations by demographic, clinical, serologic, or exposure criteria

POSSIBLE MECHANISMS BY WHICH KNOWN GENETIC RISK FACTORS MAY CAUSE AUTOIMMUNE DISEASES

- Gene products process and then bind target autoantigens with high affinity and select for other gene products that can interact with these complexes
- Gene products are unable to eliminate one or more exogenous pathogens
- Gene products result in dysregulation of normal immune responses
- Identified genes are linked to yet uncharacterized genes that are the primary risk factors for AID and affect autoantigen binding, elimination of foreign antigens, or immune system regulation
- Other mechanisms than those above - possibly involving modulation of autoantigen availability, presentation, or immunogeniticy

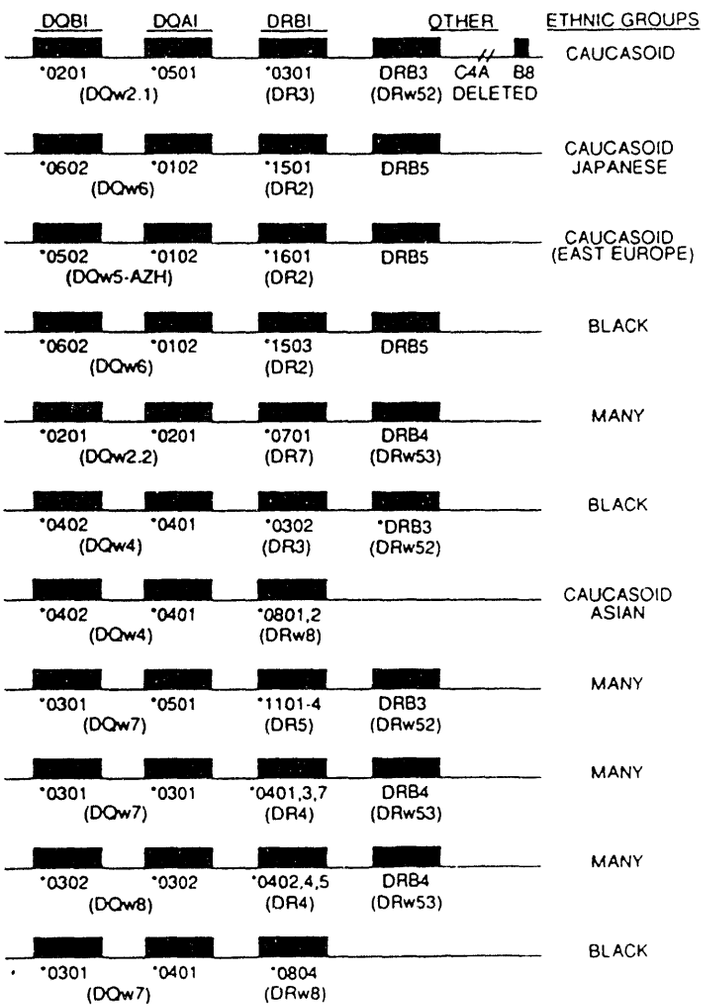

Figure 2. Selected HLA class II (DR and DQ) haplotypes are shown. Numerical designations directly under each loci (i.e., *0201, etc) are specific *alleles*. HLA *specificities* encoded by the alleles are indicated in parentheses under each allele (DRB1) or set of alleles (DQA1 and DQB1).

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SPECIFIC GENETIC FACTORS ASSOCIATED WITH AUTOIMMUNE DISEASES

- Major histocompatability complex (MHC) genes
  - Class I, II and III (complement) genes
  - Transporter associated with antigen processing (TAP) genes
- T cell receptor (TCR) genes
- Immunoglobulin (Gm and Km) genes
- Sex chromosome genes
- Minor histocompatability genes
- Cytokine genes
- Genes regulating metabolism of drugs and toxins

CONFOUNDERS IN THE STUDY OF THE GENETICS OF AUTOIMMUNE DISEASES (AID)

- Multifactorial etiologies that include genetic and environmental factors
- Heterogeneity of etiologies and pathogenesis within all defined AID syndromes
- The polygenic nature of AID
- Linkage dysequilibrium among genetic risk factors inherited as haplotypes
- Gender, ethnic, and racial differences in risk factors
- Disease-associated alleles are common in the normal population
- Stochastic events that alter the immune system and its responses over a lifetime

Table 1. Revised Criteria for the Classification of Systemic Lupus Erythmatosus*

Criterion		Definition	
1.	Malar rash		Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2.	Discoid rash		Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3.	Photosensitivity		Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4.	Oral ulcers		Oral or nasopharyngeal ulceration, usually painless, observed by physician
5.	Arthritis		Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
6.	Serositis	a)	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion
			OR
		b)	Pericarditis—documented by ECG or rub or evidence of pericardial effusion
7.	Renal disorder	a)	Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed
			OR
		b)	Cellular casts—may be red cell, hemoglobin, granular, tabular, or mixed
8.	Neurological disorder	a)	seizures—in the absence of offending drugs or known metabolic derangements; e.g., uremia,ketoacidosis, or electrolyte imbalance
			OR
		b)	Psychosis—in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9.	Hematologic disorder	a)	Hemolytic anemia—with reticulocytosis
			OR
		b)	Leukopenia—less than 4,000/mm^3 total on two or more occasions
			OR
		c)	Lymphopenia—less than 1,500/mm^3 on two or more occasions
			OR
		d)	Thrombocytopenia—less than 100,00/mm^3 in the absence of offending drugs
10.	Immunologic disorder	a)	Positive LE cell preparation
			OR
		b)	Anti-DNA: antibody to native DNA in abnormal titer
			OR
		c)	Anti-SM: presence of antibody to Sm nuclear antigen
			OR
		d)	False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11.	Antinuclear antibody		An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any four or more of the 11 criteria are present, serially or simultaneously, during an interval of observation

From Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus (SLE). Arthritis Rheum 25:1271–1277, 1982.

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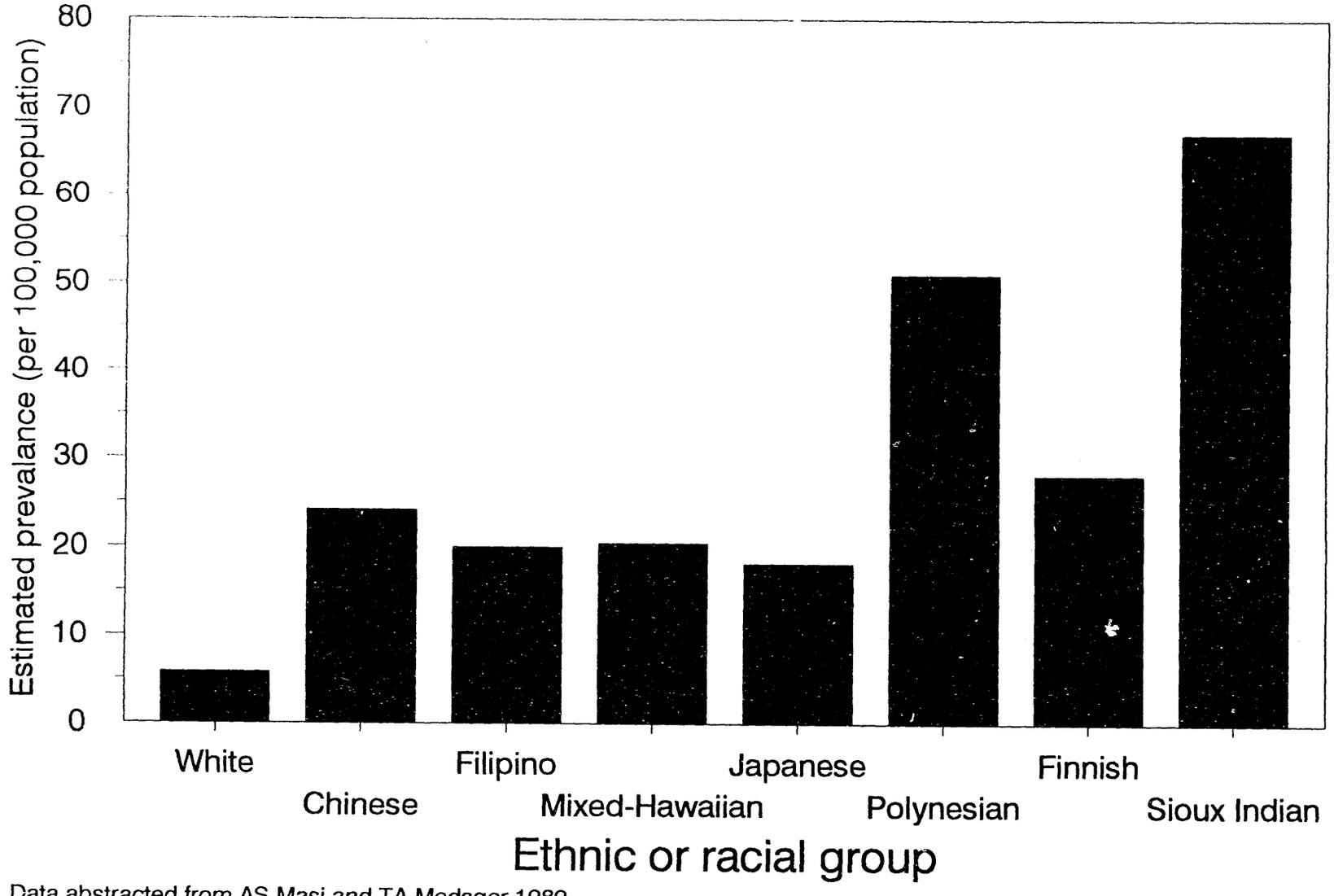
PREVALENCE OF SLE DIFFERS AMONG ETHNIC GROUPS



Data abstracted from AS Masi and TA Medsger,1989

EVIDENCE FOR THE ROLE OF GENETIC FACTORS IN THE DEVELOPMENT OF AUTOIMMUNE DISEASES (AID)

- Increased prevalence/incidence of AID in certain families
- Increased prevalence/incidence of AID in certain racial and ethnic groups
- Higher frequency of AID in monozygotic than dizygotic twins
- Specific gene products that regulate immune responses are associated with AID
- Animal studies

Frederick W. Miller, M.D., Ph.D.

IMMUNOGENETICS OF AUTOIMMUNE DISEASES

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I. Introduction

II. Distinctions between autoimmunity and autoimmune diseases
- A. Autoimmunity as a normal physiologic consequence of aging and other processes
- B. Autoimmune diseases (AID) as heterogeneous pathologic syndromes represented by complex traits

III. Reasons for considering genetic factors in the etiology of AID
- A. Increased prevalence and incidence of AID in certain families
- B. Increased prevalence and incidence of AID in ethnic/racial groups
- C. Higher frequency of AID in monozygotic than dizygotic twins
- D. Strong associations of AID with specific genes and their products
- E. Animal studies

IV. Confounders in the study of the genetics of AID
- A. Multifactorial etiologies that include genetic and environmental factors
- B. Heterogeneity of etiologies and pathogenesis within clinically defined AID syndromes
- C. The polygenic nature of AID
- D. Linkage disequilibrium among genetic risk factors inherited as haplotypes
- E. Gender, ethnic, and racial differences in risk factors
- F. Disease-associated alleles are common in the normal population
- G. Stochastic events alter the immune system and its responses over a lifetime

V. Specific gene products associated with AID
- A. Major histocompatibility (MHC) genes
  1. Class I (HLA-A,-B and -C) genes
  2. Class II (HLA-DR, DQ, and DP) genes
  3. Class III genes encoding complement components
  4. Transporters associated with antigen processing (TAP) genes
- B. T cell receptor (TCR) genes
- C. Immunoglobulin (Gm and Km) genes
- D. Sex chromosome-linked genes
- E. Minor histocompatibility genes
- F. Cytokine genes
- G. Genes regulating metabolism of drugs and toxins

VI. Possible mechanisms by which known genetic risk factors may cause AID
- A. Gene products process and then bind target autoantigens with high affinity and select for other gene products that can interact with these complexes
- B. Gene products are unable to eliminate one or more exogenous pathogens
- C. Gene products result in dysregulation of normal immune responses
- D. Identified gene products are linked to yet uncharacterized genes that are the primary risk factors for AID and whose products affect autoantigen binding, elimination of foreign antigens, or immune system regulation
- E. Other mechanisms than those above - possibly involving modulation of autoantigen availability, presentation, or immunogenicity

VII. Approaches to the study of the genetics of AID
- A. Descriptive population studies
- B. Case-control analyses of frequencies of specific genes and their products
- C. Family studies
- D. Sib-pair analyses
- E. Reverse genetic molecular approaches
- F. Phenotype-genotype correlations after subsetting AID populations by demographic, clinical, serologic, or exposure criteria

VIII. Approaches to obtain more homogeneous AID groups for studies of genetic risk factors
- A. Using demographic features
  1. Age at disease onset
  2. Gender
  3. Race/ethnicity
- B. Using clinical features
  1. Severity of disease
  2. Specific sign-symptom-pathologic complexes
- C. Using serologic features
  1. Autoantibodies shared by other diseases
  2. Disease-specific autoantibodies
- D. Using known environmental exposures
- E. Combinations of the above

IX. Environmental agents implicated in triggering AID in humans and animals
- A. Infectious agents
  1. Bacteria
  2. Viruses
  3. Parasites
- B. Non-infectious agents
  1. Drugs
  2. Foods and dietary supplements
  3. Occupational and other toxic exposures
  4. Foreign cells - graft versus host disease
  5. Medical devices - exposure to foreign materials such as silicone and collagen implants

X. Summary, conclusions and future directions

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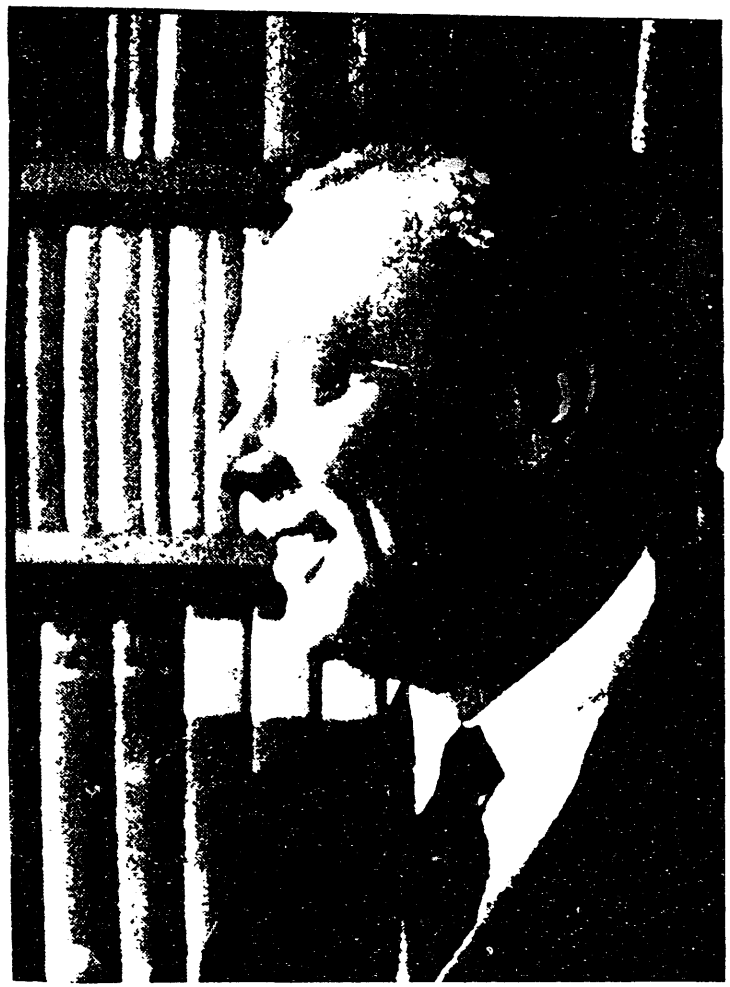
Portrait Gallery I to R. Grubb: Perspectives .....

Karl Landsteiner

Ludwik Hirszfeld

Portrait Gallery II to R. Grubb: Perspectives .....



Rob Race

Alexander Wiener

Phil Levine

Rune Grubb: Perspectives and Future Directions

I am the oldest member and the organizers have honored me by asking for my views on perspectives and future directions in immunogenetics in relation to human disease prediction and perhaps prevention.

The questions that arise are really two fundamental questions of existentialism

1. Where did we come from?
2. Where are we going?

Let me declare at the outset that I think I know where we came from, to some extent by personal experience. I do not hesitate to state that the way ahead will offer some exciting outlooks.

Historical Perspective

The foundation of interaction between immunology and genetics was laid by Karl Landsteiner's discovery of the ABO blood groups in 1900. Immunogenetics was born in 1910 when von Dungern and Hirszfeld established the Mendelian nature of the A and B blood characters. In 1925 Bernstein interpreted the data correctly. It thus took a quarter of a century to grasp the genetics of the ABO system. Ever since these crucial early studies it has been the rule to establish the genetics of any polymorphic system, be they blood groups, allotypes or histocompatibility markers. It is recorded that when Landsteiner and Levine had found the MN blood groups in 1929 they sought the help of Thomas Hunt Morgan, pioneer of genetics and Nobel laureate, in working out the inheritance.

The recognition of the Rh blood groups and of their clinical effects was a significant advance in the 1940:s and Landsteiner was again the pioneer.

In my opinion, (see Grubb 1989) it is hard to overestimate the importance of our knowledge in the Rh field, with regard to the evolution of immunogenetics. The discoveries were intensively followed up all over the world. Important groups centred around Rob Race at the Lister Institute, around Levine, and around Wiener. The cooperation of geneticists, e.g. Sir Ronald Fisher, was again sought. It was my good fortune to work at the Lister Institute in 1948, and I can bear witness to the liveliness of scientific activity there in the hey-day of Rh research with such persons as Rob Race, Ruth Sanger, Arthur Mourant and Walter Morgan on the staff. There was a constant shuttling to and fro visitors and co-workers among whom the distinctive profiles of Fisher and Coombs were often to be seen. Amongst these activities and the rampant controversies they sometimes engendered - and not only about nomenclature - some important milestones stand out:

1. Coombs' concept and the knowledge of anti-immunoglobulins.
2. The notation of close genetic linkage between the genes of the Rh system, foreshadowing what we today call genetic disequilibrium.
3. Clinically successful modification of an immune response in Rh prevention. Lewis Thomas cites this prevention as one of the very few examples of high technology in Medicine.

The allotypes of human immunoglobulins were detected in 1956 using human incomplete anti-Rh as detector molecules in a modified Coombs' test.

Among the workers in the blood group field Jean Dausset was very productive. His detection of the Mac antigen in leucocytes in 1958 is of course the first solid cornerstone established for the HLA system. So this is where we came from.

The way ahead

The organizers of our conference have for the first time I think, made HLA - and immunoglobulin Mendelian polymorphism research a joint venture. Good reason for this grip is to be found in the study of de Vries, Erna van Loghem, van Rood and others in 1979. Our Dutch friends studied descendants of Dutch colonists who emigrated to Surinam in 1845 and survived epidemics of typhoid, yellow fever etc. with a mortality of 60%. The gene frequencies for 26 polymorphic traits were compared between the Surinam descendants and the descendants of those of the religious group who stayed in Holland. It was observed that the gene frequencies significantly differed for only 3 of the 26 polymorphisms. It is no surprise to you that these 3 are HLA, Gm and complement factor 3. So our common ground is that we deal with exquisitely polymorphic systems of survival value related to effector molecules of the immune system.

The proceedings on these 2 days have highlighted the many ramifications of our subject. It is of course not my intention to try to summarize or be comprehensive. I will focus on 2 scenarios of the way ahead.

We already have a glimpse of the first scenario particularly perhaps as to the HLA situation. It is easy to recognize that we will be more successful in our predictions and preventive measures when we can precisely relate polymorphic variants to particular functions and pathophysiological events. Studies to find the relevant antigens in for example Insulin Dependent Diabetes, in myasthenia and in rheumatoid arthritis via their precise HLA ligand are well under way. The promiscuity of the combining groove as now defined is lessened when the HLA peptides are more precisely delineated.

The recent knowledge that the activity of Natural Killer cells as related to HLA-C is a promising lead to pathophysiology.

It is now a comfort to those of us working in the Ig allotype field that the human allotypes are confined to the Fc part of the molecule because all functions of Ig except antigen binding are dependent on this part. As known complement activation, Fc receptor binding, placental passage, the release of cytokines etc. are strictly related to Ig class or subclass. A first task is to find such physiological relationships related to allotypes. This is so because the allelic exclusion phenomenon means that Ig producing clones are confined not to one Ig class or subclass only but precisely to one allo-haplotype. An important start has been made: Ig G subclass levels are clearly related to the allotype constitution of the person. When it comes to the Ig G3 subclass the effect is so pronounced that the so called normal level cannot be defined without a knowledge of G3m markers (Seppälä et al. 1993).

The knowledge of idiotypes, antiidiotypes and idiotype suppression gave rise for Jernes' network theory. Dray demonstrated allotype suppression in 1962, 10 years before idiotype suppression was shown. Despite this, the story of an allotype - anti-allotype network has not yet been written. This is perhaps due to greater complexity here. We now know that we have a host of Fc receptors on varied cells of the immune system and on several species of bacteria. And quite recently anti-Fc-receptor antibodies have been shown. The prerequisites for a network is indeed at hand:
We have 1. The allotypic Fc markers 2. Anti-allotypes and rheumatoid factors 3. Fc receptors on B cells, T cells, macrophages 4. Anti-Fc receptor antibodies and 5. also "external" Fc receptors on pathogenic bacteria and viruses. Polymorphism is a characteristic trait for the Fc markers and also for the Fc receptors. I predict that restrictions analogous to those for the HLA system will be found for this network also.

I believe that we can expect a surprise scenario at the next turn of the road. I predict that we will see that genes or gene segments determining allotypic specificities, Gm or HLA for example, may be transported from one person to another with viruses as vectors. Provided that the genes express themselves, this is akin to a minor transplantation and may lead to a break of tolerance and autoimmunization. Some seemingly paradoxical observations regarding Ig allotypes and antiallotypes, particularly in rheumatoid arthritis, can be explained by such transfer. (Grubb & Kjellén 1989, Grubb 1991). From the very start

of the Gm system in 1956 it has been clear that specific anti-Gm's commonly occur in R.A. and such anti-Gm's were a prerequisite for the recognition of these allotypes. The first paradox is that in rheumatoid arthritis the anti-Gms are frequently exquisitely specific for foreign individuals' allotypes. In a recent study of anti-allotypes to Ig G3 markers in appropriately selected RA patients we found that 23 were allospecific as against 1 autospecific. (Cfr also Grubb et al. 1991). This is paradoxical because RA is by consensus an autoimmune disease.

The allotypes are of course bona_fide Mendelian traits being useful in forensic medicine. Nevertheless non-nominal allotypes, so to speak "forbidden by Mendelian law", occasionally appear in several species, including Man. This is the second remaining paradox brought to light by Ig allotype research. The gene segments determining the classical IgG1, IgG2 and IgG3 allotypes are contained in the segments which are excised in the normal SWITCH process. The proposition that these gene segments may be transferred by viruses readily accomodates or explains both of these seeming paradoxes. As known, several herpesviruses latently infect B-cells. The next SLIDE shows same reported homologies between herpesviruses and molecules of immunological interest, particularly immunoglobulins and HLA sequences. Some of these are striking, comprising several hundreds of aminoacids. The observations particularly as regards IL-10 have induced Sugden (1991) to categorize herpesviruses as transducing viruses.

It is generally accepted that retroviruses may occasionally transport host genes and the classical example is of course the tumor promoter genes (Bishop 1981). Mammary tumor virus integration as related to superantigens is a novel ramification. A novel example of particular interest in our context is that the functionally important region gp 120 of HIV virus shows significant aminoacid sequence motives with the antigen recognition site of most HLA class I C alleles. (Lopalco et al. 1993 a.o.) Slott observed in 1991 that in SIV vaccine trials anti-cell antibody titers correlated better with protection than virus neutralizing antibody titers. This paradox recently led Shearer, Clerici and Dalgleish ~~recently~~ (1993) to suggest that alloimmunization with HLA antigens be used as a vaccine against HIV. Clearly Slotts' and Fidis paradox and the 2 paradoxes of Ig allotype research mentioned have not yet been resolved at the factual level. Immunoglobulins and their Mendelian allotypic markers may serve as a model for studying the occurrence and consequences of such hijack and transfer:

The reasons are

1. Ig genes, their sequences and regulation are thoroughly known.
2. The Mendelian polymorphism of the human IgHC genes is well worked out and understood at the molecular level. Sequence correlates of several allotypes are simple and precisely known.
3. In the Ig switch process, defined Ig gene sequences coding for allotypes are excised from the genome. DNA ring formation simplifies their study (and may conceivably facilitate viral hijacking).

The fact that anti-Gm's with allospecificity are common in RA adds interest for studying this model.

CODA

I started with the historical perspective and pointed to the importance of progress as regards Rh for the evolution of immunogenetics. When it comes to risk assesment Rh is an ideal example: Our routine tests do this perfectly. And what is more: we can prevent new cases by applying practically simple measures. This is so successful that this high technology is almost regarded as commonplace. The basis is that we can precisely relate the polymorphic variants as to function and as to pathophysiological events. Let this live example from our history be our guiding star. We cannot set a higher goal.

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Slide 1

Components of an Ig allotype - anti-allotype - Fc-receptor network

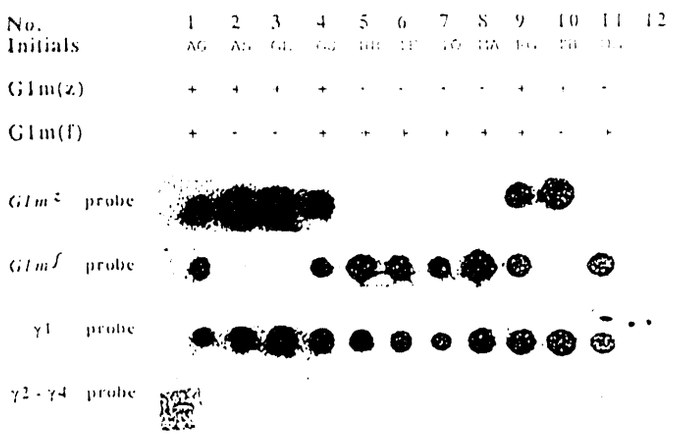
1. Ig Fc allotypes
2. Anti-allotypes and Rheumatoid Factors
3. Fc-receptors on immune cells
4. Antibodies to Fc-receptors
5. Fc-receptors on bacteria and viruses

Table 2.

. Some homologies between human nucleotide sequences and those in the herpes virus family

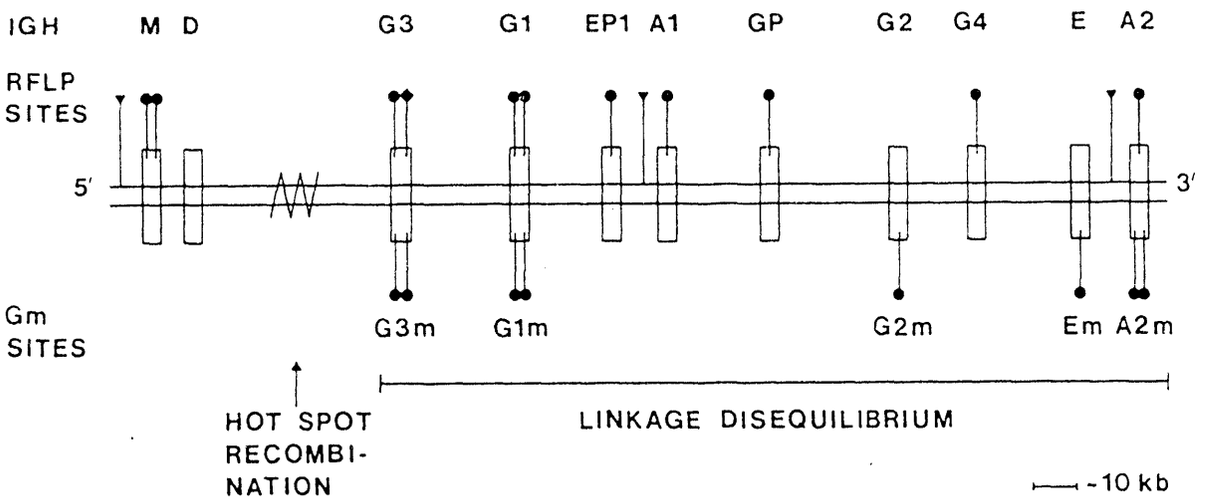
Homo	Herpes	Comment	Reference
Ig switch	H. simplex		Gomez-Marques et al. (1985)
Ig switch	Epstein-Barr		Freese et al. (1983)
Ig, IgG1C	Epstein-Barr	BARF-1, EC-LF4	Wang et al. (1989, 1991)
Ig, IgG1C	Epstein-Barr	QQBE-1	Cashman & Pouliot (1990)
HLA-A2	Cytomegalo	Extensive	Beck & Barrell (1988)
HLA-DQw8	Epstein-Barr	BOLF-1	Sarirenji et al. (1991)
HLA-DR4	Epstein-Barr	gp110	Roudier et al. (1988)
HLA-DR β chain	Cytomegalo	15 amino acids	Fujinami et al. (1988)
CD19	Epstein-Barr	QQBE 21	Stamenkovic & Seed (1988)
C3 DG	Epstein-Barr	gp 350	Nemerow et al. (1987)
IL-10	Epstein-Barr	BCRF-1	Moore et al. (1990)
		Extensive	Vieira et al. (1991)
G protein-coupled receptors	Cytomegalo	Extensive	Chee et al. (1990)
Hydrofolate reductase	H. saimiri	Extensive	Trimble et al. (1988)
Thymidylate synthase	H. saimiri	Extensive	Bodemer et al. (1986)

FIGURE 3. R.GRUBB:RECENT ADVANCES IN IMMUNOGLOBULIN GENETICS



Determination of allelic genes *Glm*^{f} and *Glm*^{z} by subclass-specific amplification of DNA and allele specific probes. The results of conventional typing are recorded above the dot-blots. (From Balbin et al., 1991.)

FIGURE 3 R.GRUBB:RECENT ADVANCES IN IMMUNOGLOBULIN GENETICS



Schematic physical map of the human IgH "constant" gene cluster. The positions of polymorphic RFLP and Gm sites are indicated. Symbols: ● at least dimorphic site in genes or pseudogenes; ▼ at least dimorphic site in the switch region; ◆ at least dimorphic site in the hinge region.

TABLES TO R. GRUBB: s PRESENTATION: RECENT ADVANCES IN IMMUNOGLOBULIN GENETICS

Table 1

Basic Data on Main Gm Markers

Marker	a	b	c	f	g	z	x	t	u	v	x	r
IgG subclass	1	3	3	1	3	2	3	3	3	3*	1	1
IgG domain CH	3	Fc	3	1	Fc	Fc	3	3	2	3	3	1
Frequency (%)												
in whites	35–85	80–95	<1	80–95	35–85	80–95	<1	<1	~100	>95	15–30	35–65
in Mongols	~100	Widely variable	<1	Widely variable	Widely variable	80–95	35–60	10–30	>95	>95	5–40	20–65
in blacks	~100	~100	10–60	<1	<1	<1	>95	<1	100	>95	<1	?

*In IgG1 in some blacks.

Table 2

Amino Acid and Codon Substitutions Correlating With Glm and Km Allotypes

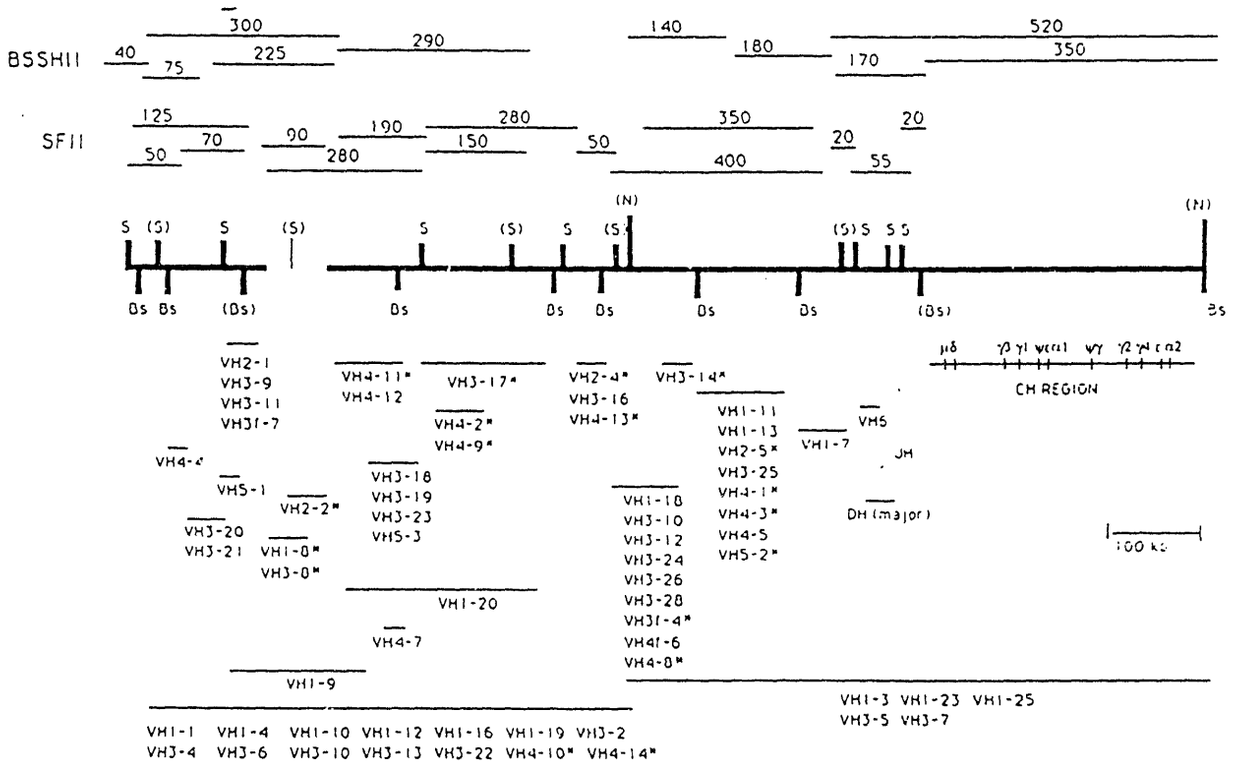
Allotype		Amino acid and residue (Eu numbering)		Codon	
Glm	a	Asp	Leu	GAT	CTG
		356	358		
"Non-a"	a–	Glu	Met	GAG	ATG
Glm	f	Lys		AAA	
		214			
Glm	z	Arg		AGA	
Glm	x	Gly		GGT	
		431			
Glm	–(x)	Ala		GCT	
Km	1, 2	Ala	Leu		
		153	191		
Km	1, –	Val	Leu		

Table 3.

RFLPs of the Human Ig HC Gene Cluster

Investigators	Restriction enzyme	Probe derived from	Number of polymorphic sites	Observed haplotypes combined with Gm markers	Location in genome	Special feature
Beech-Hansen et al., 1983	*Bam*HI	γ_4	4		γ_2, γ_4, $\delta\gamma$	
Migone et al., 1983	*Sst* I	μ switch	6	≥32	μ switch, α_1 switch	
Migone et al., 1985	*Pvu* II				α_2 switch, $\delta\varepsilon$	
Lefranc and Rabbitts, 1984	*Eco*RI	α_2	2		α_2	Detects A2m allotypes precisely
	Pst I					
Johnson et al., 1986	*Mbo* I	γ_1 and others	≥5	82	μ, γ_3, γ_1, γ_2,	
	*Bst*EII		8		$\delta\gamma_3$, α_1, α_2	
Ghanem et al., 1988a	*Bam*HI				γ_3, γ_1, γ_2, γ_4,	
Ghanem et al., 1988b	*Sac* I	γ_3, γ_1 hinge	≥15	≥180	$\delta\gamma$	Specific IgG3 hinge probe
	*Eco*RI					
Ghanem et al., 1989	*Bst*EII also	γ_3, γ_1 hinge	≥5 additional			
Jazwinska et al., 1988	*Pvu* II + *Taq* I	γ_4	14			
Benger and Cox, 1989	*Apa* I	δ	3		δ–μ switch	
	Xba I					
	Taq I					
Balbin et al., 1994	*Nsp* BII	γ_1	2		γ_1	Detects G3m(b) and G3m(g) Subclass-specific amplification required
	Rsa I					

FIGURE 1 R.GRUBB:RECENT ADVANCES IN IMMUNOGLOBULIN GENETICS



Physical map of the human immunoglobulin heavy chain gene cluster. V_H gene segments known to be polymorphic are indicated by an asterisk. BSHII and Bs indicate fragments and cleavage sites obtained with *Bss*HII. SFII and S indicate fragments and cleavage sites with *Sfi*I, ignoring the numerous sites in the C_H region. N indicates known *Not* I fragment sites. The scale is shown at the lower right. (From Walter et al., 1990.)

APPROACHES TO OBTAIN MORE HOMOGENEOUS GROUPS FOR STUDIES OF AID GENETIC RISK FACTORS

- Using demographic features
  - Age at disease onset
  - Gender, race, ethnicity
- Using clinical features
  - Severity of disease
  - Specific sign-symptom-pathologic complexes
- Using serologic features
  - Autoantibodies shared by other diseases
  - Disease-specific autoantibodies
- Using known environmental exposures
- Combinations of the above

T[redacted]I. DQ Beta First Domain Amino Acid Sequences

	10	20	30	40	50	60	70	80	90	
	RDSPEDFVYQ	FKGLCYFTNG	TERVRGVTRH	IYNREEYVRF	DSDVGVYRAV	TPQGRPVAEY	WNSQKEVLEG	ARASVDRVCR	HNYEVAYRGI	LQRR
Not associated with antitopo I										
DQw5;DQB1*0501	----------	---M------	-----L-S-S	------I---	-----EF---	-LL-L-A---	-----DI--R	K--A------	---QLEL-TT	----
DQw2,DQB1*0201	----------	----------	----------	----------	----------	------S---	----------	----------	----------	----
DQw5;DQB1*0502	----------	----------	----------	----------	----------	------D---	----------	--------		
DQw5;DQB1*0503			--------	----------	----------					
Possibly associated with Antitopo I (DQB1 alleles found in HLA-DQw3-negative, antitopo I-positive PSS patients)										
DQw4;DQB1*0402	--------F-	---M------	-----G---Y	-------A--	----------	--L--LD---	-----DI--E	D-----T---	---QLEL-TT	----
DQw6;DQB1*0601	--P-----L-	--AM------	-----Y---Y	------D---	----------	------D---	-----DI--R	T--EL-T---	------F---	----
DQw6;DQB1*0602	--------F-	---M------	-----L---Y	-------A--	----------	------D---	----------	T--EL-T---	------F---	----
DQw6;DQB1*0603			---L----	-------A--	----------	------D---	----------	T--EL-T-		
DQw6;DQB1*0604	----------	---M------	-----L----	-------A--	----------	----------	---------R	T--EL-T---	-----G----	----
Associated with antitopo I										
DQw7;DQB1*0301	----------	--AM------	-----Y---Y	-------A--	----E-----	--L-P-D---	---------R	T--EL-T---	---QLEL-TT	----
DQw8;DQB1*0302	----------	---M------	-----L---Y	-------A--	----------	--L-P-A---	---------R	T--EL-T---	---QLEL-TT	----
DQw9;DQB1*0303	----------	---M------	-----L---Y	-------A--	----------	--L-P-D---	---------R	T--EL-T---	---QLEL-TT	----

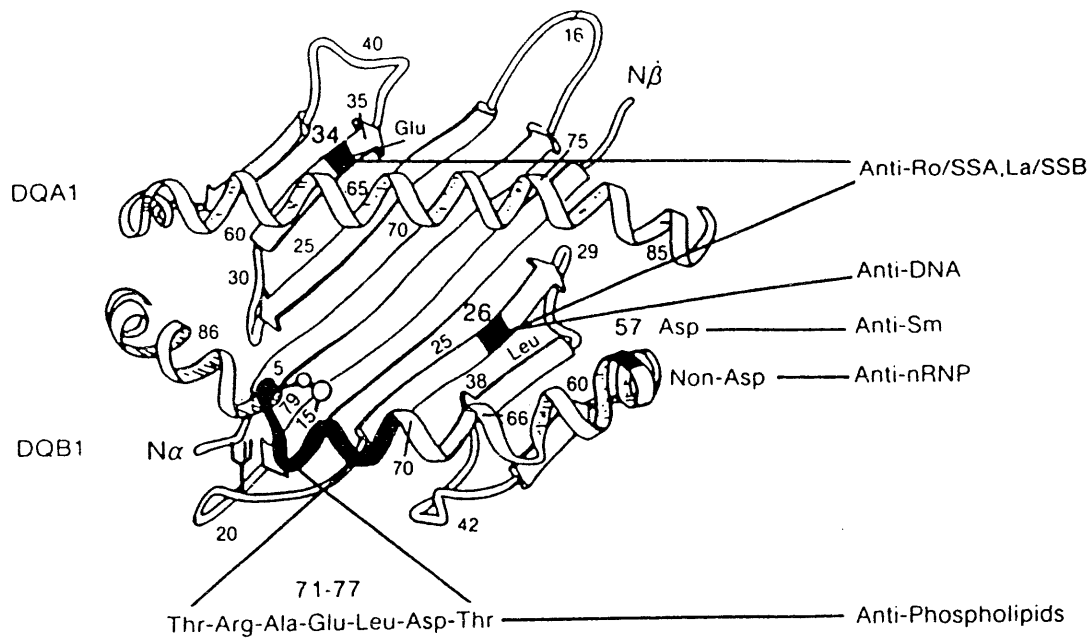


Figure 4. Schematic representation of the model proposed by Brown et al[29] for class II MHC structure adapted for HLA-DQ molecules. Numbers indicate outermost domain amino acid positions (from Fig. 3). Specific amino acid positions showing the strongest associations with selected lupus autoantibodies are highlighted.

From: F.C. Arnett et al. 1992, Rheum. Dis. Clinics N. America **18**:865-892

IDIOPATHIC INFLAMMATORY MYOPATHIES (IIM)

- A group of rare, heterogeneous, connective tissue diseases which share chronic muscle inflammation.
- Criteria for diagnosis include: Muscle weakness, elevated serum CK levels, characteristic rashes, EMG, and muscle biopsy findings.
- Etiologies are unknown but environmental and genetic factors are associated with certain clinical and serologic groups.
- Pathogenesis appears to be related to humoral and/or cellular immune mechanisms.

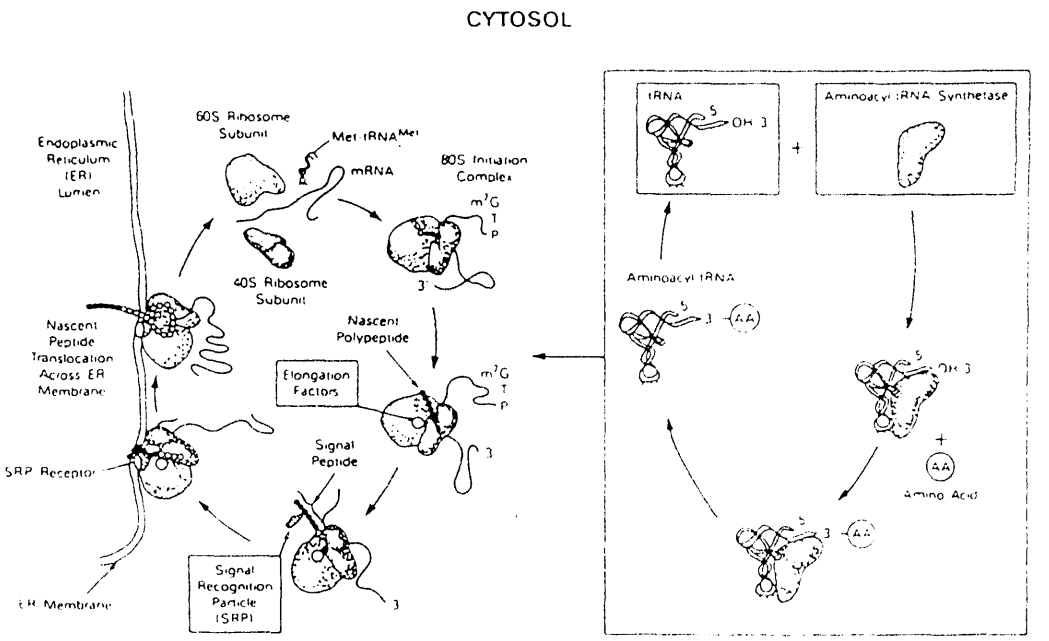
IDIOPATHIC INFLAMMATORY MYOPATHIES

Clinical Classification	Serological Classification
• Primary polymyositis • Primary dermatomyositis • Myositis overlap with another connective tissue disease • Cancer-associated myositis • Juvenile dermatomyositis • Inclusion body myositis	• Myositis-specific autoantibody + Anti-synthetase autoantibodies Anti-SRP autoantibodies Anti-Mi-2 autoantibodies Anti-MAS autoantibodies Others • Myositis-specific autoantibody -

CHARACTERISTICS OF THE MYOSITIS-SPECIFIC AUTOANTIBODIES

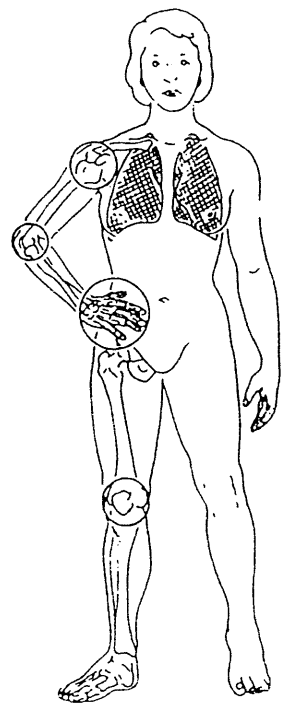
- They tend to be directed against conserved conformational epitopes on phosphorylated cytoplasmic ribonucleoprotein particles involved in translation
- The protein moiety of the complex is usually the antigenic target
- They inhibit the function of the protein they target by in vitro assays
- They appear to arise months before myositis onset, are antigen-driven, and vary in titer with myositis disease activity

TARGETS OF THE MYOSITIS-SPECIFIC AUTOANTIBODIES



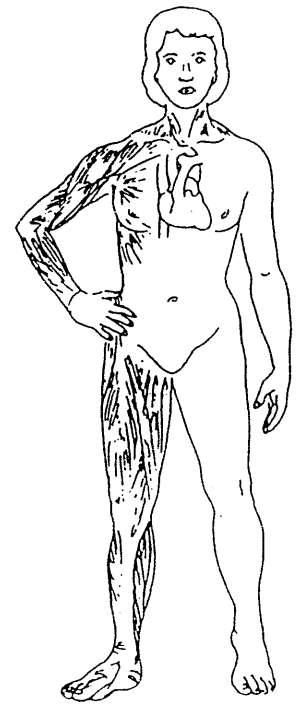
IIM SEROLOGIC GROUPS DIFFER IN CLINICAL FEATURES

ANTI-SYNTHETASE



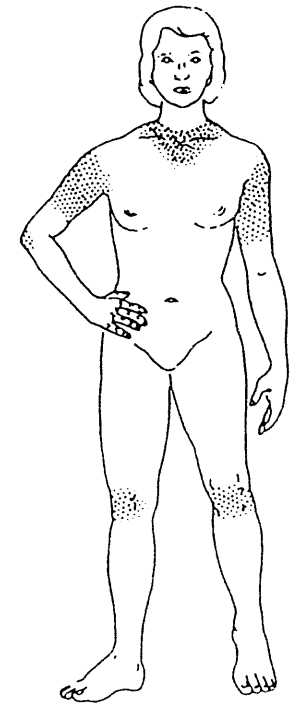
- Interstitial lung disease
- Arthritis
- Mechanic's hands
- Fever

ANTI-SRP



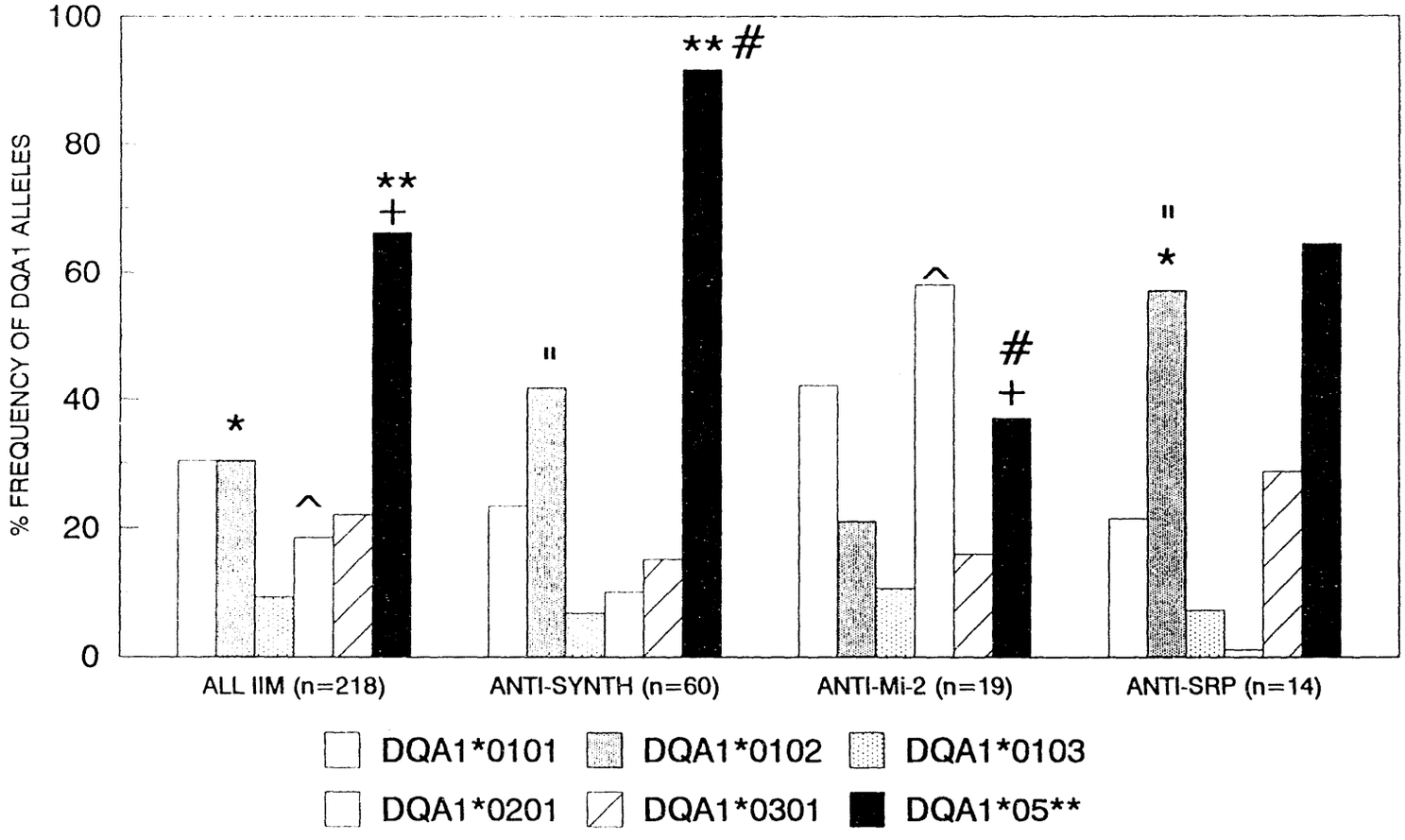
- Acute severe muscle weakness
- Cardiac involvement
- Myalgias

ANTI-Mi-2



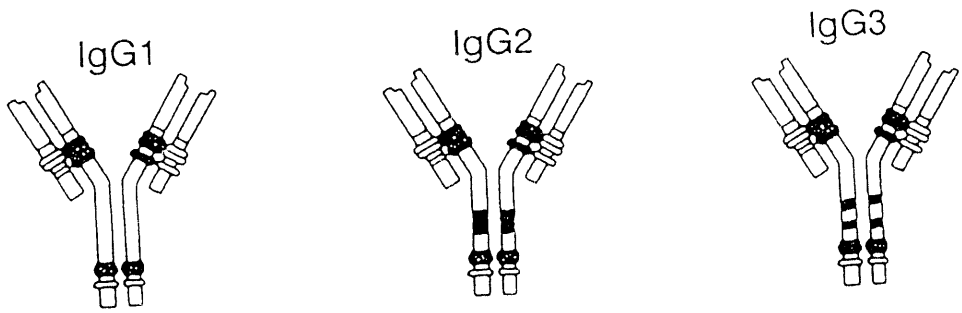
- V-sign rash
- Shawl-sign rash
- Cuticular overgrowth

FREQUENCY OF DQA1 ALLELES IN MYOSITIS PATIENTS GROUPED BY MYOSITIS-SPECIFIC AUTOANTIBODIES



Symbols above bars depict significant ($P < .05$) differences

DIFFERENT IgG SUBCLASSES HAVE DIFFERENT ALLOTYPES WHICH TOGETHER DEFINE Gm PHENOTYPES



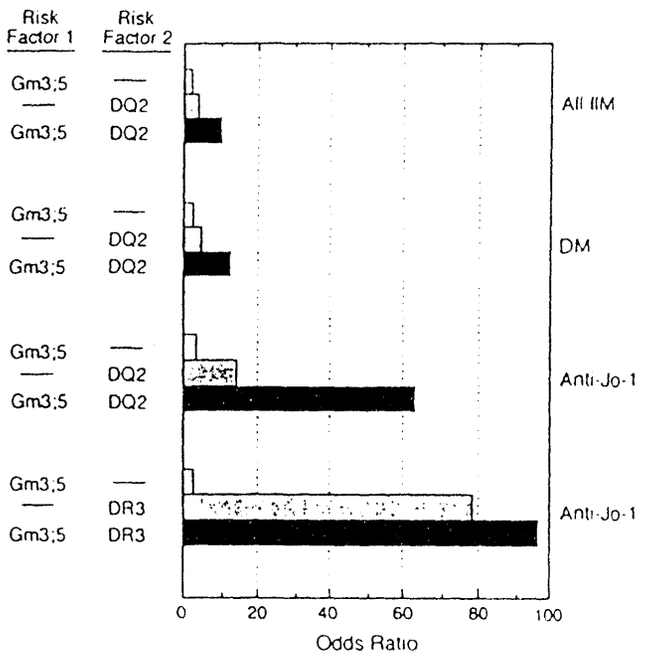
	IgG1	IgG2	IgG3
Gm allotypes	1,17	23	5,13

Example of a Gm phenotype: Gm (1,3,17;23;5,13,21)

GENETIC RISK FACTORS ASSOCIATED WITH IIM

Gene Locus	All IIM	Serologic Groups		
		Anti-Synthetase	Anti-SRP	Anti-Mi-2
HLA DRB1	*DRB1*0301*	*DRB1*0301*	*(DRB1*0501)*	*DRB1*0701*
HLA DQA1	*DQA1*0501*	*DQA1*0501*	*DQA1*0102*	*DQA1*0201*
IGHG1-3 (GM)	Gm 3;5	Gm 3;5	Gm 1,17;5,6	(Gm 3;23;5)

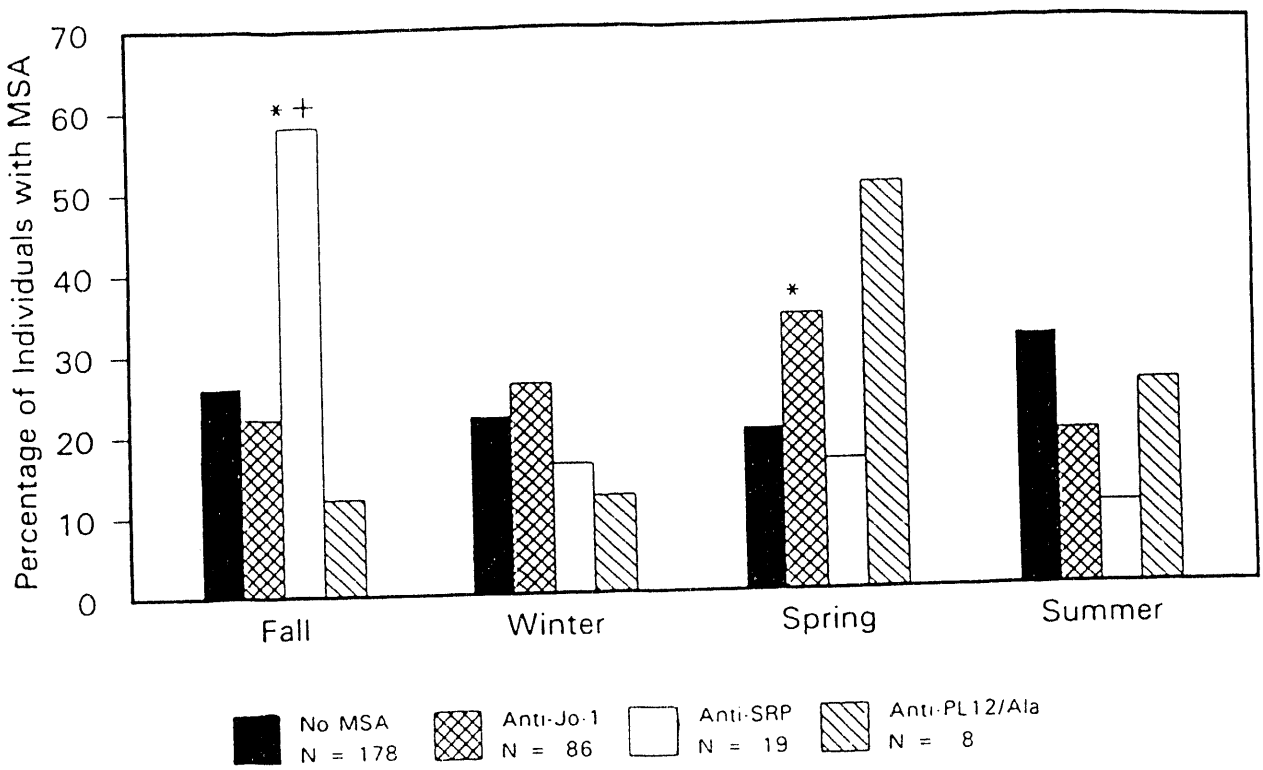
Interactions of Gm 3;5 and MHC Class II alleles in conferring risk for the development of myositis (all IIM), dermatomyositis (DM), and myositis-specific autoantibodies to histidyl-tRNA synthetase (anti-Jo-1) in white patients. All odds ratios were calculated in the context of the combination depicted.



GENETIC RISK FACTORS FOR MYOSITIS

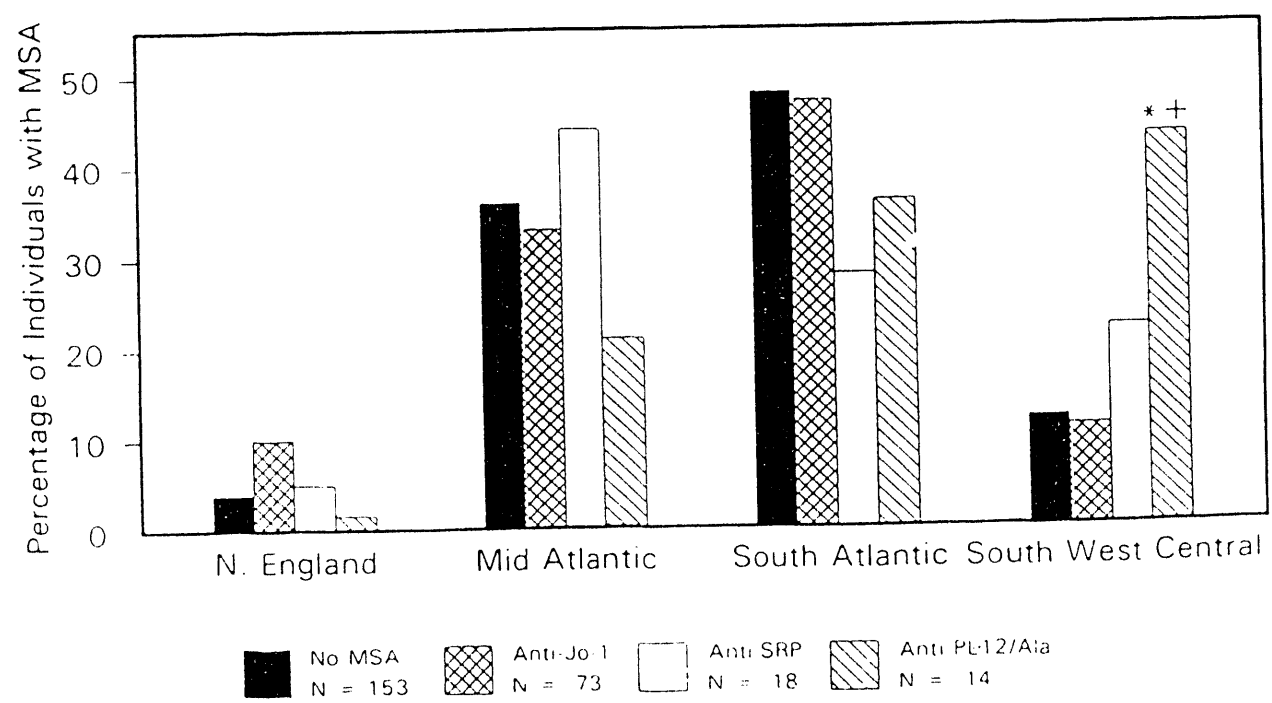
- Genes within or linked to 2 loci are associated with development of myositis
  - The MHC locus on chromosome 6 - specifically HLA-DRB1 and HLA-DQA1 genes
  - The GM locus on chromosome 14 - genes encoding immunoglobulin G heavy chains whose products are serologically defined as Gm phenotypes
- Different alleles at each locus are associated with different clinical and serologic groups
- MHC and GM alleles, or closely linked genes, interact to increase risk for the development of myositis and some of the clinical and serologic subgroups

SEASON OF IIM ONSET IN SEROLOGICAL GROUPS



* P < 0.05 compared to no MSA
+ P < 0.05 compared to Anti-Jo 1 Group

GEOGRAPHICAL DISTRIBUTION OF IIM ONSET IN SEROLOGICAL GROUPS

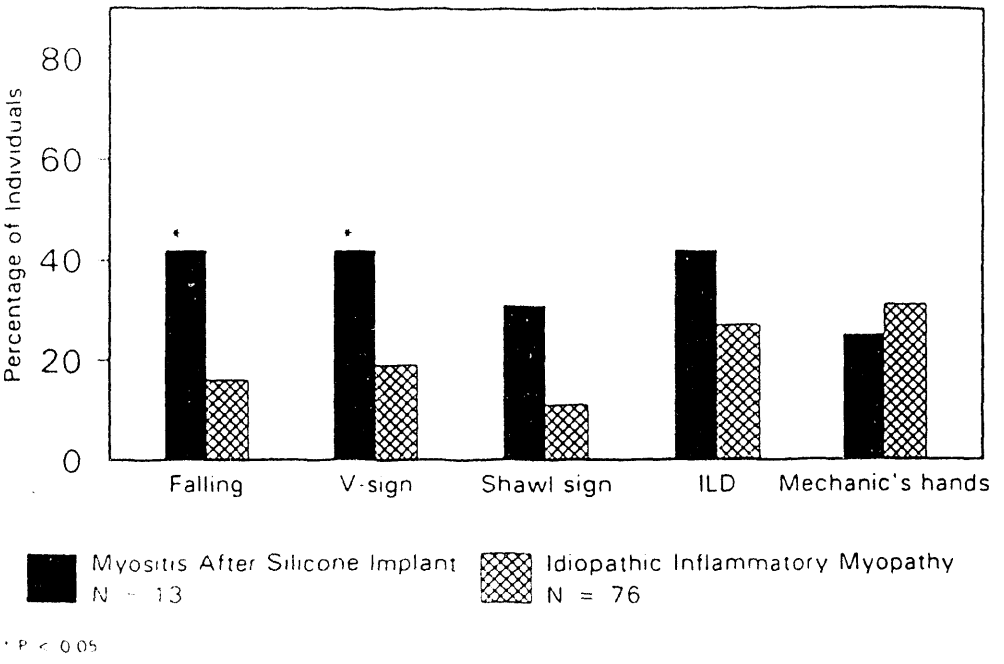


* P < 0.05 compared to no MSA
+ P < 0.05 compared to Anti-Jo 1 Group

INFLAMMATORY MYOPATHIES CLASSIFIED ON THE BASIS OF KNOWN ENVIRONMENTAL EXPOSURES

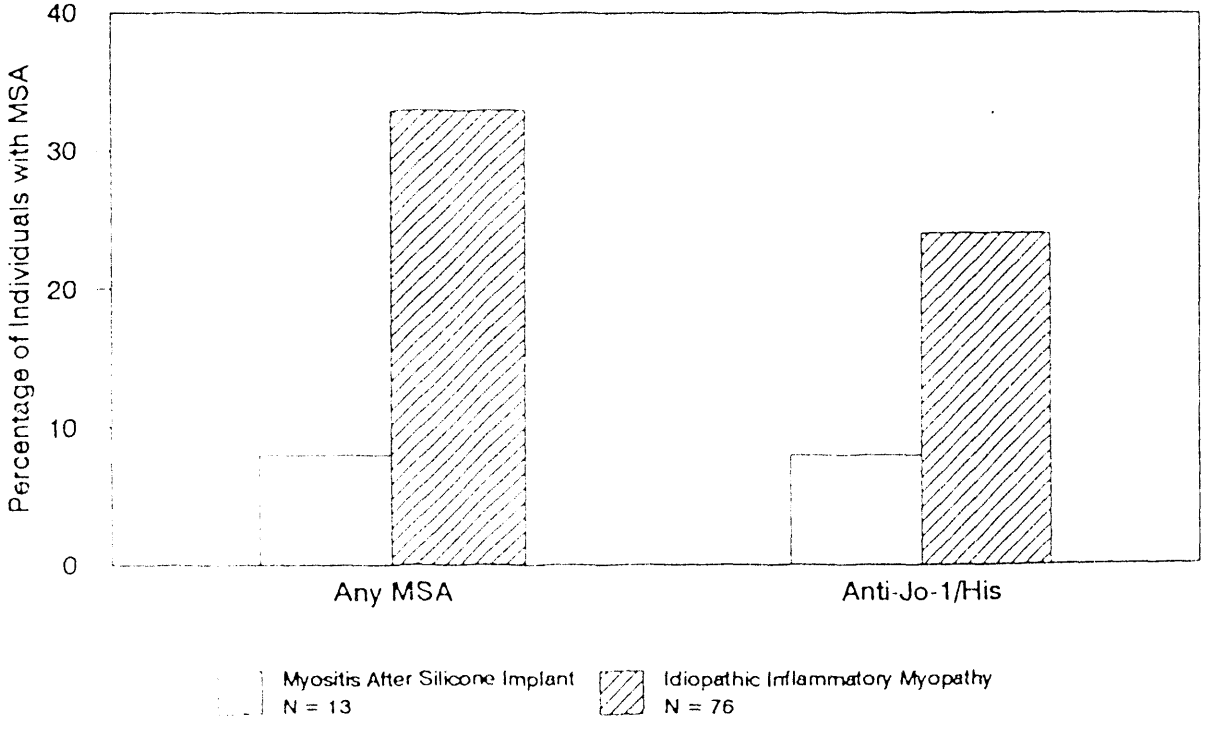
- Drug-associated myositis
  - D-penicillamine
  - Others including cimetidine, leuprolide acetate, procainamide and hydralazine
- Dietary-associated myositis
  - Adulterated rapeseed oil (as part of the toxic oil syndrome)
  - L-tryptophan (as part of the eosinophilia myalgia syndrome)
  - Ciguatera toxin
- Occupational-associated myositis
  - Silica and possibly vinyl chloride
- Device-associated myositis
  - Silicone and collagen implants

Frequency of selected symptoms and signs differ among white women with myositis after silicone implants and women with myositis without silicone exposure.

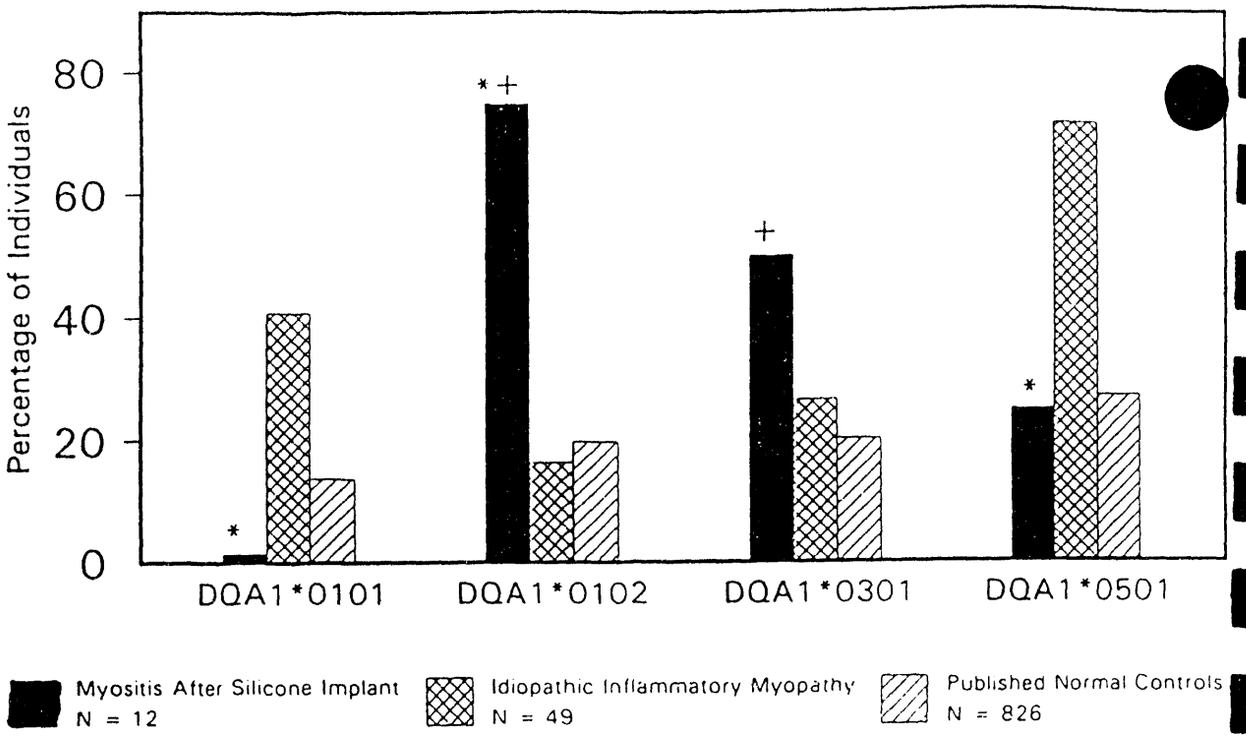


* P < 0.05

Frequency of certain autoantibodies differ among white women with myositis after silicone implants, women with myositis without silicone exposure.



Frequency of selected HLA-DQA1 alleles differ among white women with myositis after silicone implants, women with myositis without silicone exposure, and normal controls.



* P < 0.05 compared to IIM Patients
+ P < 0.05 compared to Normal Controls

CONCLUSIONS

- Patients who develop myositis after silicone implants differ from those with idiopathic myositis in certain clinical, serologic and immunogenetic features.
- The presence of HLA DQA1*0102 or closely linked genes may be a genetic risk factor for the development of myositis after silicone implants.
- Further studies of larger groups of patients and appropriately matched controls are needed to define these findings more fully.

ENVIRONMENTAL AGENTS IMPLICATED IN TRIGGERING AUTOIMMUNE DISEASES IN HUMANS AND ANIMALS

- Infectious agents
  - Bacteria
  - Viruses
  - Parasites
- Non-infectious agents
  - Foods and dietary supplements
  - Drugs
  - Occupational and other toxic exposures
  - Foreign cells - graft versus host disease
  - Medical devices - foreign materials such as silicone and collagen implants

POSSIBLE MECHANISMS FOR THE DEVELOPMENT OF AUTOIMMUNE DISORDERS

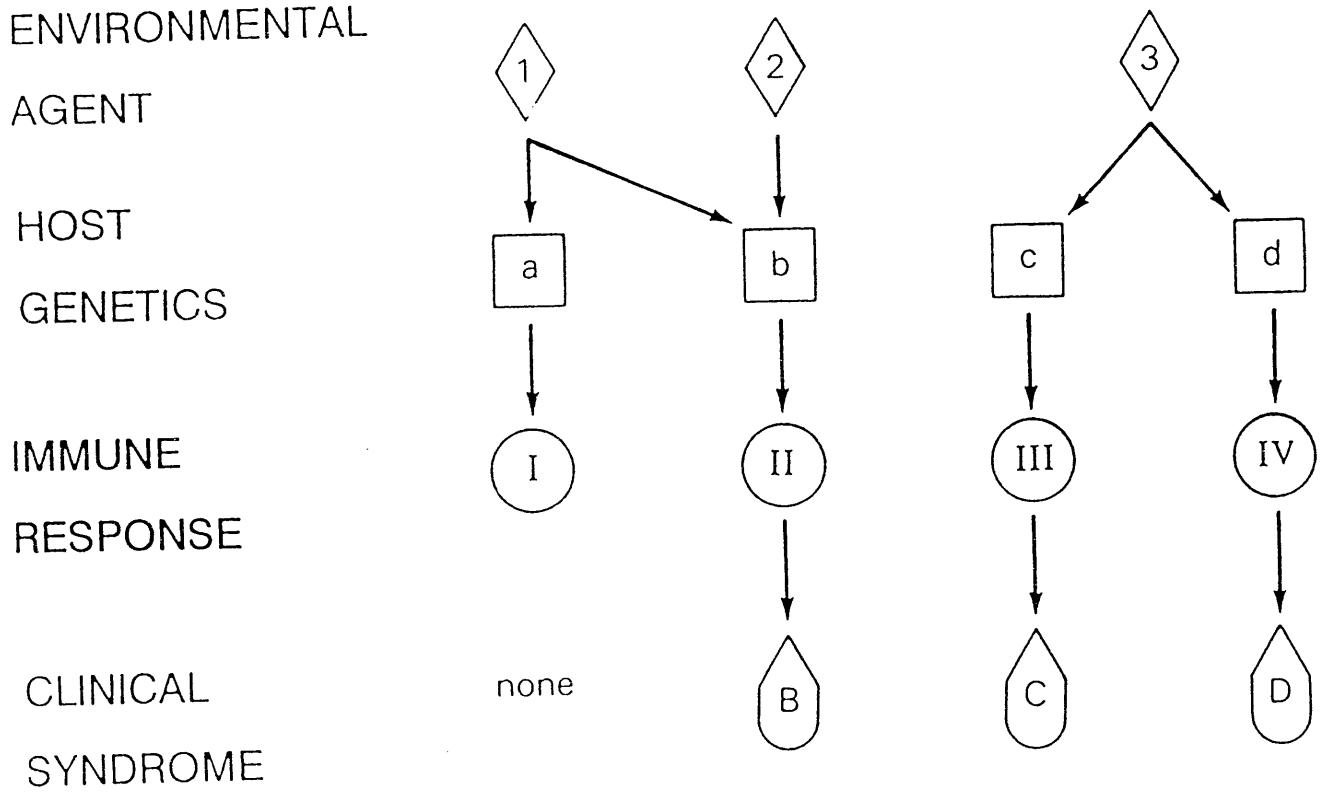


Table 5.4 HLA Associations with Systemic Autoimmune Connective Tissue Disease

Disease	HLA antigen associations	"Primary" MHC associations
Systemic lupus erythematosus	DR2, DR3, C4A*QO	? C4A*QO
Anti-Ro and La	DR2, DR3; DQw1/DQw2	DQα2/DQβ2(DQw2.1) and DQα6/DQβ6(DQw6) trans combinations
C2-deficient lupus (anti-Ro)	A25, B18, DR2	C2*QO
Anti-nDNA	DR2	?DQw6
Anti-procollagen 7	DR2	Unknown
Anti-U1-RNP	?DR4; neg DQw1/DQw2	Unknown
Sjögren's syndrome	DR3, DRw52	Unknown
Anti-Ro and La	DR2, DR3, DQw1/DQw2	DQα2/DQβ2(DQw2.1) and DQα6/DQβ6 (DQw6) trans combinations
HIV associated	DR5 (JVM) (blacks)	DRβ1 third diversity region
Juvenile dermatomyositis	B8, DR3, C4A*QO	Unknown
Polymyositis	DR3	
Anti-Jo-1	DR3, DR5, DRw6, (DRw8(DRw52)	?DRβ1 first diversity region
Scleroderma	DR1, DR5, DR3, DRw52, C4A*QO, C4B*QO	Unknown
Anti-Scl 70 (topoisomerase I)	DR5	Unknown
Anti-centromere	DR1, DR4, DRw8	Unknown
Anti-PM-Sci	B8, DR3	Unknown
Rheumatoid arthritis	DR4, DR1	DRβ1 third diversity region

From: Reveille, J.D. and Arnett, F.C. (1991) Immunology Series **54**:97-140

Table 5.6 HLA Associations with Other Autoimmune Diseases

Disease	HLA antigen associations	"Primary" MHC associations
Type I diabetes mellitus	DR3, DR4, DQw8	DQβ position 57
Pemphigus vulgaris	DR4 (Dw10) DRw6, DQw1.19	DRβ1 third diversity region DQβ position 57
Pemphigus foliaceous	DR1, DQw1 DR4 DQw3	Unknown
Epidermolysis bullosa acquisita	DR2, DQw1	Unknown
Dermatitis herpetiformis and celiac disease	DR3, DR5, DR7, DQw2 DPw1, ?DPw3	DQα2, DQβ2 DPβ/positions 56, 57, 69
Myasthenia gravis	B8, DR3	Unknown
Narcolepsy	DR2	DR2
Multiple sclerosis	DR2	?DQβ6, DQβ8, DQβ9
Graves' disease	B8, DR3	Unknown
Hashimoto's thyroiditis	B8, DR3	Unknown
Ankylosing spondylitis	B27, B7	HLA-B
Reiter's syndrome	B27, B7	HLA-B
Behçet's disease	B51	Unknown
Takayasyu's arteritis	B52	Unknown
Psoriasis	B13, B17, B37, Cw6	Unknown

From: Reveille, J.D. and Arnett, F.C. (1991) Immunology Series **54**:97-140

Janardan P. Pandey, Ph.D.

Immunoglobulin Allotype-Associated Immune Responsiveness

1. Genetic control of immune response
2. Immunoglobulin allotype-linked/associated immune response genes
3. Km(l) immunoglobulin allotype and antibody response to immunization with *Haemophilus influenzae* type b polysaccharide-pertussis vaccine and risk of *Haemophilus* meningitis
4. G2m(23) immunoglobulin allotype and IgG subclass responses to *Haemophilus influenzae* type b polysaccharide vaccine
5. Gm phenotypes and *Haemophilus influenzae* type b disease in children vaccinated with type b polysaccharide vaccine
6. Antibody response to the conjugate vaccine is not allotypically restricted
7. Ig allotypes and immune response to type III group B streptococcal antigen
8. Km locus and humoral immunity to *Campylobacter jejuni*
9. Gm allotype influence on the antibody response to the outer membrane proteins of a common upper respiratory tract organism, *Moraxella catarrhalis*.
10. Ig allotypes and antinuclear antibodies in patients with connective tissue diseases
11. Ig allotypes and humoral immunity to osteosarcoma
12. Possible mechanisms
13. Evolutionary significance

David N. Propert, Ph.D.

Immunoglobulin Allotypes and RFLPs in Disease Association

David Propert

Department of Applied Biology and Biotechnology
Royal Melbourne Institute of Technology
Melbourne, Australia

The marker Gm(a), forerunner of a series of highly polymorphic immunoglobulin allotypes, was discovered as a result of a chance observation in the laboratories of Professor Rune Grubb (Grubb, 1956; Grubb and Laurell 1956).

The serum of a person being tested for immunoglobulin level was found to contain an antibody that agglutinated the anti-D-coated red cells being used as indicators but not uncoated cells. Importantly, it was found that the antibody, subsequently called anti-Gm(a), was inhibited by the sera of 60% of Swedish blood donors, called Gm(a+), but not by sera of 40%, called Gm(a-). Family studies showed the Gm(a+) phenotype was produced by a dommant gene called Gm^a and that Gm(a-) people were homozygous for the recessive allele *Gm*.

A European population investigation (Grubb, 1961) found a marked north-south decreasing cline in the frequency of Gm^a. Strikingly, the frequency of the Gm(a+) phenotype, in most of the countries sampled, was the same as the latitude of the capital city of that country (TABLE 1)

The principle of immunoglobulin allotyping by serology is illustrated in FIGURE 1. Type O, Rh +ve red cells are coated with an incomplete anti-D antibody known to be positive for the allotype of interest. The coated cells are mixed with an antiserum against the allotype in question which has been previously mixed with serum from the person being tested. Inhibition of agglutination indicates that the test serum is positive for the particular allotype.

In my laboratory, we use a 0.1% suspension of coated red cells and perform our allotyping in microtitre plates (FIGURES 2 and 3).

In the years following the discovery of Gm(a), an extensive number of additional allotypes were described (FIGURE 4). Of these, the Gm and Km systems have been most extensively studied in investigations of population genetics and disease association.

Gm allotypes are inherited in fixed combinations called haplotypes. Different human populations are each characterised by a small number of common haplotypes (FIGURE 5). This means, that for studies of different racial groups, different allotypes will be chosen. For example, for studies of Caucasian populations, we type for G1m(1), G1m(2), G1m(3), G2m(23), G3m(5) and Km(1).

As well as racial differences in common Gm haplotypes, most populations show marked clines in haplotype frequencies. Some of these are illustrated in FIGURES 6-8 taken from the remarkable compilation by Steinberg and Cook (1981).

I will now return to the topic of this presentation and address some studies of disease association. This is an enormous field. Soon after their discovery, the Gm and Km polymorphisms, along with the HLA system, became candidate genes for the study of susceptibility to immune-related human disease. This interest predates the current fashionability of candidate genes by several decades.

The groups of diseases most extensively studied for Gm and/or Km associations include autoimmune disorders, malignancies and infectious diseases. For the present discussion, I would like to concentrate on three autoimmune diseases - multiple sclerosis (MS), insulin-dependent diabetes mellitus (IDDM) and systemic lupus erythematosus (SLE). Those interested in a more general overview are referred to Whittingham and Propert (1986).

Three studies have addressed the roles of Gm allotypes in susceptibility to MS (TABLE 2). As none of these investigated G2m(23), five common Gm phenotypes were detected in each -

1. Gm (1,17;21)
2. Gm (1,2,17;21)
3. Gm (1,3,17;5,10,11,13,14)
4. Gm (1,2,3,17;5,10,11,13,14)
5. Gm (3;5,10,11,13,14)

The three studies found essentially consistent patterns in Gm frequencies but seemingly slight differences resulted in divergent interpretations.

Some populations are obviously less than ideal for studies of this type. The Melbourne gene pool, for example, is largely of UK origin but has substantial contributions from most other parts of Europe. MS has a well documented cline in prevalence, decreasing in frequency from north to south in the northern hemisphere (like the frequency of *Gm*$^{1,17;21}$ and *Gm* $^{1,2,17;21}$). One obviously must be very careful to avoid ethnographic stratification between patients and controls in such studies. Superimposed on this is the fact that MS risk is probably more related to a person's country of residence in early years rather than the origin of his or her genes.

Turning now to SLE, a disorder that Professor Pandey's group has studied extensively, we again find a complex situation. Present results (TABLE 3A) suggest that various genetic mechanisms may be acting in different populations and that susceptibility may result from interaction of HLA and Gm - linked genes. The results of the Mexican study suggest the genetics of SLE susceptibility may be clarified by the addition of immunoglobulin polymorphism detected at the DNA level to that determined serologically.

Investigations of Km in SLE (TABLE 3B) suggest that population-specific genetic susceptibility may occur and that the occurrence of specific autoantibodies may be related to immunoglobulin kappa genetics.

The results of our own investigations of Gm and Km allotypes in two populations in Kuala Lumpur are shown in more detail in TABLES 3C and 4.

Studies of IDDM have also produced confusing results. Investigation of Melbourne patients has suggested an interaction of Gm allotypes with HLA DR3 or DR4 in susceptibility.

Before addressing diabetes in more detail, I would like to diverge a little from the serology and discuss how allotype analysis may be complemented by analyses at the DNA level.

The discovery of a G2m(23) - positive, IgG2, anti-Rh antibody by Dugoujon *et al.*(1989) made G2m(23) allotyping as simple as for the other Gm allotypes. Previously, G2m(23) could only be typed by coupling a G2m(23) - positive myeloma protein to red cells using chromium chloride, a technique which, in my hands, was difficult and unreliable. As each of the three common Caucasian haplotypes may or may not have Gm^{23} , its inclusion increases the possible number of Gm genotypes from six to 21. Ten phenotypes are recognisable (TABLE 5). The common Caucasian phenotype Gm (3;23;5,10,11,13,14) is produced by two serologically indistinguishable genotypes. In my laboratory, we use RFLP analysis using the enzyme *Pvu*II and an IgG4 probe to distinguish these and other genotypes as the Gm^{23} gene element is almost always accompanied by bands of 7 and 2 kb while its absence is marked by a 9 kb band in Caucasians (FIGURE 9).

Km analyses (TABLE 6) can be similarly extended using PCR amplification and RFLP analysis (FIGURES 10 and 11) as developed by Professor Moxley of Virginia (Moxley and Gibbs, 1992) or PCR amplification and allele-specific oligonucleotide probing (FIGURE 12) (Kurth *et al.* 1991).

Returning now to IDDM, I would like to present some recent data from some Melbourne patients (TABLE 7). There is a significantly increased frequency of the Km(1-) phenotype in the diabetes patients compared to that in an ethnographically matched series of controls. Serologically determined Gm phenotypes, however, show no significant difference. When classified according to G2m(23) serology and *Pvu*II RFLP (we call this allogenotyping) there is a marked difference between patients and controls (TABLE 8). When sub-divided according to sex, the G2m(23) allogenotype association is found to be limited to male patients. When sub-divided according to HLA DR3 and DR4 phenotype, the association is found in only those patients positive for DR4. These results suggest that IDDM susceptibility may be increased by a recessive gene in positive linkage disequilibrium with Gm^{23} that interacts with HLA DR4 and has a greater effect in males.

The studies that I have reviewed in this presentation seem to suggest that Gm and Km allotypes, themselves, may not influence disease susceptibility but the associations found may reflect linkage disequilibrium with other polymorphisms of the constant region genes or with specific variable region genes. This latter possibility is supported by evidence of allelic association of Km and V kappa B3 (Moxley and Gibbs, 1992).

In conclusion, my co-workers and I believe that future studies in this area should use DNA analysis to complement or even replace serological typing and should try to concentrate on genetically homogeneous populations in many racial groups. Concurrent HLA analysis may enhance such studies and family studies should be included when possible.

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TABLE 1
EUROPEAN FREQUENCES OF GM(1)
Grubb (1961)

POPULATION	GM(1)	CAPITAL	LATITUDE
Lapland	67%	Kiruna	67°
Sweden	60	Stockholm	60
Norway	60	Oslo	60
Denmark	55	Copenhagen	55
France	50	Paris	40
Greece	40	Athens	40

TABLE 2
GM ALLOTYPES AND MULTIPLE SCLEROSIS SUSCEPTIBILITY IN CAUCASIANS

STUDY	POPULATION	RESULT	INTERPRETATION
Pandey *et al.*(1981)	USA	Gm(1,17;21)phenotype increased in MS	Recessive gene associated with Gm* 1,17;21 haplotype
Propert *et al.*(1982)	Australia	Gm(1,17;21) and Gm(1,2,17;21) phenotypes increased in MS	Recessive gene associated with Gm*1,17,21 and Gm*1,2,17;21 haplotypes
Sandberg-Wollheim *et al.*(1984)	Sweden	Gm(3;5) phenotype decreased in MS	Dominant gene associated with Gm*1,17;21 and Gm*1,2,17;21 haploytpes

TABLE 3A
GM ALLOTYPES AND SUSCEPTIBILITY TO SLE

POPULATION	ASSOCIATION	REFERENCE
Japanese	G1m(2)	Nakao *et al.* (1980)
Negro	Gm(1,17;5,6,13)	Fedrick *et al.* (1983)
Caucasian	Gm heterozygotes,HLA-B8	Whittingham *et al.* (1983)
Caucasian	Gm(1,3;5)	Schur *et al.*. (1985) Hoffmann *et al.* (1991)
Caucasian	Gm homozygotes,HLA-B8	Stenszky *et al.* (1986)
Caucasian	No Gm or Am association	Hartung *et al.* (1991)
Mexican	Ig RFLP	Kumar *et al.* (1991)

TABLE 3B
KM ALLOTYPES AND SUSCEPTIBILITY TO SLE

POPULATION	ASSOCIATION	REFERENCE
Caucasian	Km(1), anti-La	Whittingham *et al.* (1984)
Caucasian	No Km association	Schur *et al.* (1985)
Caucasian	Km(1), anti-Sm	Hoffmann *et al.* (1991)
Caucasian	No Km association	Hartung *et al.* (1991)
Malay	No Km association	Propert *et al.* (1991)
Chinese	Km(1)	Propert *et al.* (1991)
Caucasian	No Km association	Singh *et al.* (1993)

TABLE 3C Distribution of Gm and Km Phenotypic Frequencies in Chinese and Malay SLE Patients and Controls

Phenotype	Chinese		Malays	
	SLE	Controls	SLE	Controls
Gm(1,17; ;21)	2	1	0	1
Gm(1,2,17; ;21)	2	0	0	2
Gm(1,17; ;11,13,15,16,21)	4	0	0	0
Gm(1,3,17;23;5,11,13,21)	23	22	10	6
Gm(1,3,17; ;5,11,13,21)	0	2	1	2
Gm(1,17;23;21)	0	1	0	0
Gm(1,2,17;23,21)	0	0	2	0
Gm(1,2,17; ;11,13,15,16,21)	1	0	0	1
Gm(1,2,3,17;23;5,11,13,21)	3	7	2	7
Gm(1,2,3,17; ;5,11,13,21)	0	0	0	1
Gm(1,3,17;23;5,11,13,15,16)	6	3	1	1
Gm(1,3,17; ;5,11,13,15,16)	0	1	0	0
Gm(1,3;23;5,11,13)	20	36	15	38
Gm(1,3; ;5,11,13)	1	0	0	0
Total Gm Phenotypes	62	73	31	59
Km(1+ve)	46	31	14	27
Km(1-ve)	16	43	17	34
Total Km Phenotypes	62	74	31	61

TABLE 4 Frequencies and Standard Errors of Gm Haplotypes and Km Alleles in Chinese and Malay Patients and Controls

Haplotype or Allele	Chinese				Malays			
	SLE		Controls		SLE		Controls	
	Frequency	± SE	Frequency	± SE	Frequency	± SE	Frequency	± SE
$Gm^{1,17;\ ;21}$	0.265	0.040	0.157	0.042	0.205	0.052	0.095	0.028
$Gm^{1,2,17;\ ;21}$	0.050	0.020	0		0		0.099	0.028
$Gm^{1,17;\ ;11,13,15,16}$	0.089	0.026	0.027	0.014	0.016	0.016	0.017	0.012
$Gm^{1,3;23;5,11,13}$	0.564	0.047	0.668	0.047	0.659	0.071	0.694	0.056
$Gm^{1,3;\ ;5,11,13}$	0.033	0.022	0.065	0.033	0.051	0.046	0.094	0.045
$Gm^{1,17;23;21}$	0		0.035	0.032	0		0	
$Gm^{1,2,17;23;21}$	0		0.048	0.018	0.069	0.033	0	
Km^{1}	0.492	0.045	0.238	0.035	0.260	0.056	0.253	0.039
Km^{3}	0.508	0.045	0.762	0.035	0.740	0.056	0.747	0.039

TABLE 5

GM PHENOTYPES AND GENOTYPES IN CAUCASIANS

	Phenotype detected	Phenotype inferred	Genotype	
1	Gm(1)	Gm(1,17; ;21)	$Gm^{1,17;\ ;21}$	$Gm^{1,17;\ ;21}$
2	Gm(1;23)	Gm(1,17;23;21)	$Gm^{1,17;\ ;21}$	$Gm^{1,17,23,21}$
			$Gm^{1,17,23,21}$	$Gm^{1,17,23,21}$
3	Gm(1,2)	Gm(1,2,17; ;21)	$Gm^{1,17;\ ;21}$	$Gm^{1,2,17;\ ;21}$
			$Gm^{1,2,17;\ ;21}$	$Gm^{1,2,17;\ ;21}$
4	Gm(1,2;23)	Gm(1,2,17;23;21)	$Gm^{1,17;\ ;21;}$	$Gm^{1,2,17,23,21}$
			$Gm^{1,2,17;\ ;21}$	$Gm^{1,17;\ ;23,21}$
			$Gm^{1,2,17;\ ;21}$	$Gm^{1,2,17,23,21}$
			$Gm^{1,17,23,21}$	$Gm^{1,2,17,23,21}$
			$Gm^{1,2,17,23,21}$	$Gm^{1,2,17,23,21}$
5	Gm(1,3)	Gm(1,17; ;5,10,11,13,14)	$Gm^{1,17;\ ;21}$	$Gm^{3;\ ;5,10,11,13,14}$
6	Gm(1,3;23)	Gm(1,17;23;5,10,11,13,14)	$Gm^{1,17;\ ;21}$	$Gm^{3,23;5,10,11,13,14}$
			$Gm^{1,17,23,21}$	$Gm^{3;\ ;5,10,11,13,14}$
			$Gm^{1,17,23,21}$	$Gm^{3,23;5,10,11,13,14}$
7	Gm(1,2,3)	Gm(1,2,3,17; ;5,10,11,13,14	$Gm^{1,2,17;\ ;21}$	$Gm^{3;\ ;5,10,11,13,14}$
8	Gm(1,2,3;23)	Gm(1,2,3,17;23;5,10,11,13,14)	$Gm^{1,2,17;\ ;21}$	$Gm^{3,23;5,10,11,13,14}$
			$Gm^{1,2,17,23,21}$	$Gm^{3;\ ;5,10,11,13,14}$
			$Gm^{1,2,17,23,21}$	$Gm^{3,23;5,10,11,13,14}$
9	Gm(3)	Gm(3; ;5,10,11,13,14)	$Gm^{3;\ ;5,10,11,13,14}$	$Gm^{3;\ ;5,10,11,13,14}$
10	Gm(3;23)	Gm(3;23;5,10,11,13,14)	$Gm^{3;\ ;5,10,11,13,14}$	$Gm^{3,23;5,10,11,13,14}$
			$Gm^{3,23;5,10,11,13,14}$	$Gm^{3,23;5,10,11,13,14}$

TABLE 5A

SOME GM PHENOTYPES AND GENOTYPES IN CAUCASIANS

Phenotype	Genotype
Gm (1,2,17; ;21)	$Gm^{1,2,17;\ ;21}$ $Gm^{1,2,17;\ ;21}$ $Gm^{1,2,17;\ ;21}$ $Gm^{1,17;\ ;21}$
Gm (3;23;5,10,11,13,14)	$Gm^{3;23;5,10,11,13,14}$ $Gm^{3;23;5,10,11,13,14}$ $Gm^{3;23;5,10,11,13,14}$ $Gm^{3;\ ;5,10,11,13,14}$
Gm (1,2,3,17;23;5,10,11,13,14,21)	$Gm^{1,2,17;\ ;21}$ $Gm^{3;23;5,10,11,13,14}$ $Gm^{1,2,17;23;21}$ $Gm^{3;\ ;5,10,11,13,14}$ $Gm^{1,2,17;23;21}$ $Gm^{3;23;5,10,11,13,14}$

TABLE 6
KM PHENOTYPES AND GENOTYPES

GENOTYPE	PHENOTYPE	
	SEROLOGY	DNA PCR/ASO
$Km^{1,2}$ $Km^{1,2}$	Km(1+)	Km(1,2)
$Km^{1,2}$ Km^{3}	Km(1+)	Km(1,2,3)
Km^{3} Km^{3}	Km(1-)	Km(3)
Km^{1} Km^{1}	Km(1+)	Km(1)
Km^{1} $Km^{1,2}$	Km(1+)	Km(1,2)
Km^{1} Km^{3}	Km(1+)	Km(1,3)

Table 7 Gm and Km phenotypes in diabetes patients, preclinical individuals and healthy controls.

Phenotype	Diabetes patients	Preclinical	Controls
	n	n	n
Gm(1)	2	2	1
Gm(1,2)	10	1	9
Gm(1,3; ;5)	15	2	9
Gm(1,3;23;5)	21	11	24
Gm(1,2,3; ;5)	3	4	6
Gm(1,2,3;23;5)	13	1	9
Gm(3; ;5)	3	2	10
Gm(3;23;5)	40	16	39
Total	107	39	107
Km(1+)	11	6	24
Km(1-)	96	33	83
Total	107	39	107

Gm Phenotype, Patients *vs* Controls: χ^2, 7 d.f.=7.6, p>0.05.
Preclinical Individuals *vs* Controls: χ^2, 7 d.f.=7.8, p>0.05.

Km Phenotype, Patients *vs* Controls: χ^2, 1 d.f.=5.8, p<0.025.
Preclinical Individuals *vs* Controls: χ^2, 1 d.f.=0.9, p>0.05.

TABLE 8

G2m(23) allogenotypes in type 1 diabetes patients and controls

G2m(23) allogenotype	Patients	Controls
Positive homozygotes	27	11
Heterozygotes	34	35
Negative homozygotes	9	24
Total	70	70

χ^2, 2 d.f. = 13.6, $p < 0.005$

TABLE 9

G2m(23) allogenotypes in type 1 diabetes patients (subdivided according to HLA DR3 and DR4 phenotypes) and healthy controls.

G2m(23) allogenotype	Diabetes patients											Controls		
	Females					Males					Total	Females	Males	Total
	DR3/X	DR4/X	DR3/4	DRX/X	Total	DR3/X	DR4/X	DR3/4	DRX/X	Total				
G2m(23)-positive homozygotes	2	4	1	1	8	2	8	6	3	19	27	6	5	11
G2m(23)-heterozygotes	1	3	5	2	11	6	7	8	2	23	34	14	21	35
G2m(23)-negative homozygotes	3		1		4		3	1	1	5	9	12	12	24
Total	6	7	7	3	23	8	18	15	6	47	70	32	38	70

Patients *vs* Controls: X^2, 2 d.f. = 13.6, $p < 0.005$

Male Patients *vs* Male Controls: X^2, 2 d..f. = 10.3, $p < 0.01$

Female Patients *vs* Female Controls: X^2, 2.d.f. = 3.3, $p > 0.05$

HLA DR3/X Patients *vs* Controls: X^2, 2.d.f. = 1.7, $p > 0.05$

DR4/X Patients *vs* Controls: X^2, 2 d.f. = 11.6, $p < 0.005$

DR3/4 Patients *vs* Controls: X^2, 2 d.f. = 6.3, $p < 0.05$

FIGURE 1

DIAGRAMMATIC PRESENTATION OF THE PRINCIPLE OF Gm(1) DETERMINATION

Phase 1.	**Sensitization of O D-positive erythrocytes.**	O D-positive erythrocytes. + Incomplete anti-D with Gm(1) → Coated erythrocytes sensitized with anti-D/Gm(1)	
Phase 2.	**Mixing the test serum with anti-Gm(1) antiserum.**	a) Binding of anti-Gm(1)	b) No binding of anti-Gm(1)
Phase 3.	**Testing for the inhibition of agglutination or for agglutination.**	a) Inhibition of agglutination: Gm(1)	b) No inhibition of agglutination: Gm(—1)
		SERUM Gm(1)	SERUM Gm(—1)

Anti-Gm(1) —

Incomplete anti-D with Gm(1) —

IgG from normal sera:

Gm(1) —

Gm(—1) —

FIGURE 2
GM TYPING IN MICROTITRE PLATE

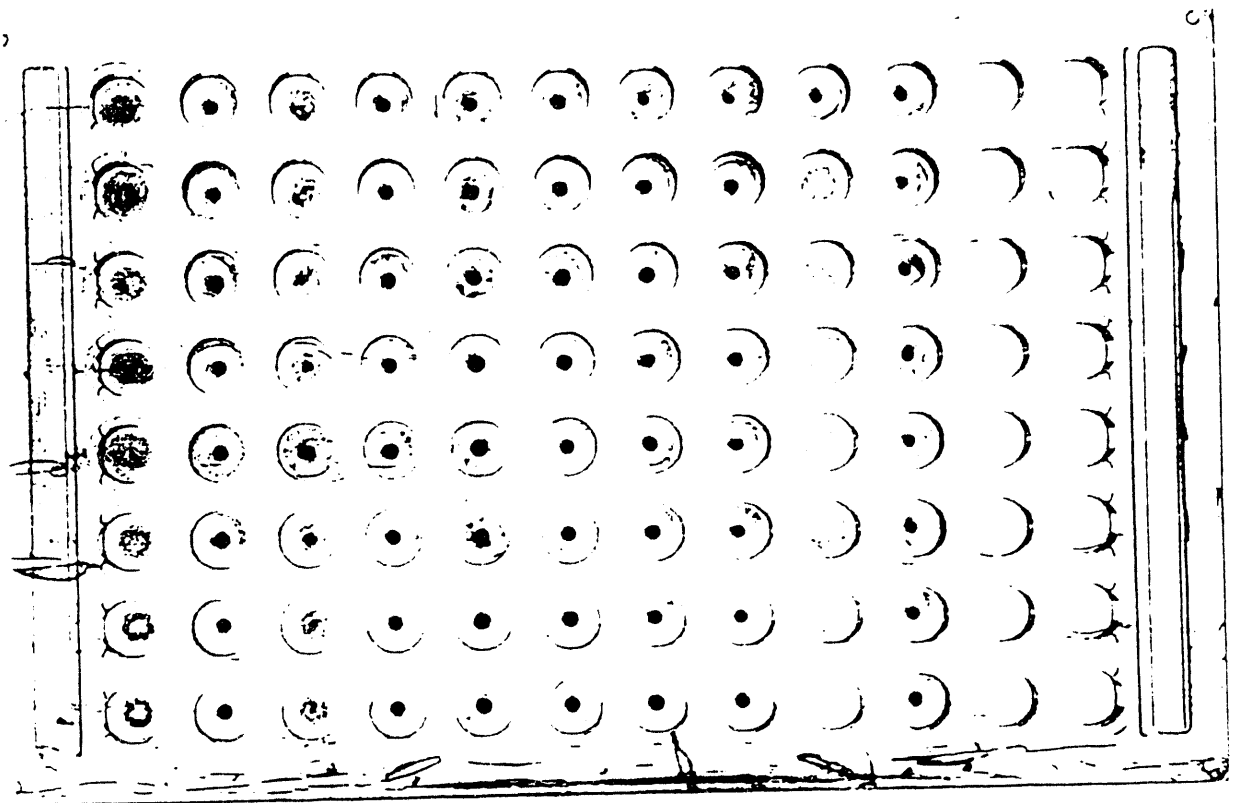
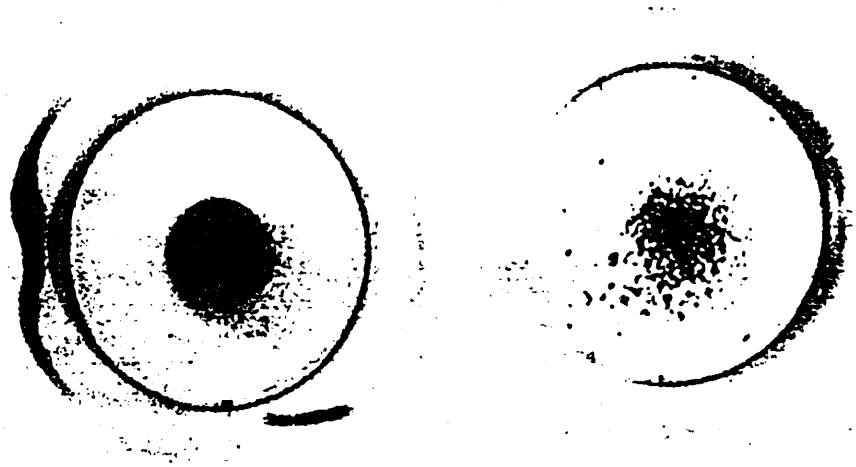


Fig. 2 Microtitre plate ready for examination. Binding of specific anti-Gm sera to test serum leads to inhibition of agglutination, i.e. a positive result. Presence of agglutination indicates antiserum lacks appropriate Gm specificity. Agglutination is readily distinguished in this tray from non-agglutination where cells form into a tight button at the bottom of well

FIGURE 3
ENLARGEMENT OF FIGURE 2



Close up view of part of Fig. 2 plate. Right well shows agglutination

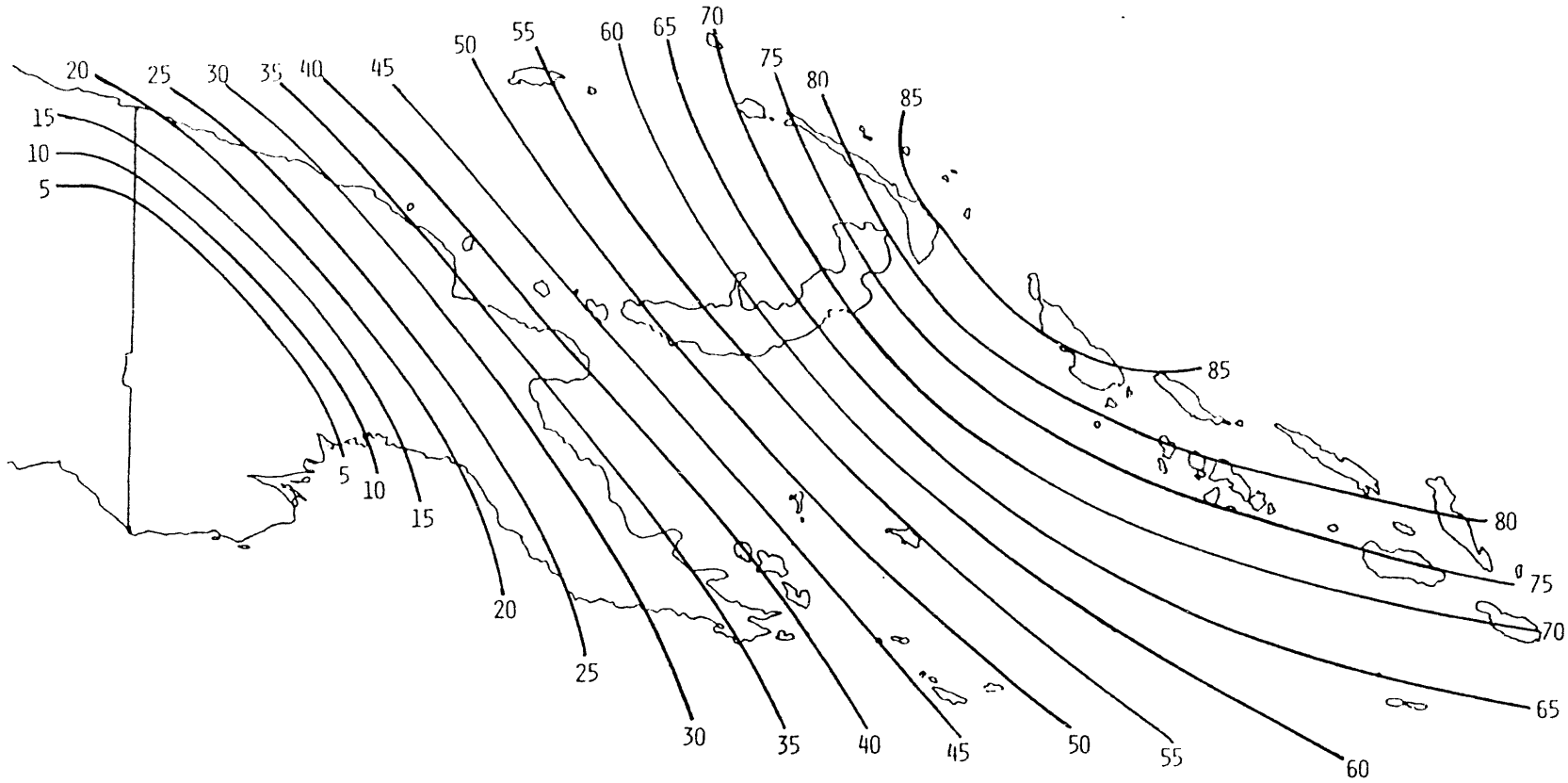
FIGURE 4
IMMUNOGLOBULIN ALLOTYPES
WHO (1976)

Location	Alphameric Designation	Numeric Designation
IgG1	G1m(a)	G1m(1)
	(x)	(2)
	(f)	(3)
	(z)	(17)
IgG2	G2m(n)	G2m(23)
IgG3	G3m(b0)	G3m(11)
	(b1)	(5)
	(b3)	(13)
	(b4)	(14)
	(b5)	(10)
	(c3)	(6)
	(c5)	(24)
	(g)	(21)
	(s)	(15)
	(t)	(16)
	(u)	(26)
	(v)	(27)
IgA2	A2m(1)	A2m(1)
	A2m(2)	A2m(2)
IgE	Em(1)	Em(1)
K Chain	Km(1)	Km(1)
	(2)	(2)
	(3)	(3)

FIGURE 5
COMMON GM HAPLOTYPES IN VARIOUS RACIAL GROUPS
Steinberg (1973)

Race	Common haplotypes
Caucasoid	(1,17,21) (1,2,17,21) (3,5,13,14) each ± 23
Negroid	(1,5,13,14,17) (1,5,14,17) (1,5,6,17) (1,5,6,14,17)
Ainu	(1,17,21) (1,13,17) (2,17,21) (1,2,17,21)
Mongoloid	(1,17,21) (1,2,17,21) (1,13,17) (1,3,5,13,14)
Bushmen	(1,17,21) (1,5,17) (1,13,17) (1,5,13,14,17)
Pygmy	(1,5,6,17) (1,5,13,14,17)
Micronesian	(1,17,21) (1,3,5,13,14)
Melanesian	
New Guinea	(1,17,21) (1,2,17,21) (1,3,5,13,14) (1,5,13,14,17)
Bougainville	(1,17,21) (1,2,17,21) (1,3,5,13,14)
Malaita	(1,17,21) (1,2,17,21) (1,3,5,13,14) (1,2,5,13,14,17)
Australian	
Aborigines	(1,17,21) (1,2,17,21)
Malayan	(1,17,21) (1,2,17,21) (1,3,5,13,14)

FIGURE 6
DISTRIBUTION OF GM*1,3,5,10,11,13,14 IN PNG
Steinberg and Cook (1981)



DISTRIBUTION OF GM- 1,3,5,10,11,13,14 IN EASTERN ASIA
Steinberg and Cook (1981)

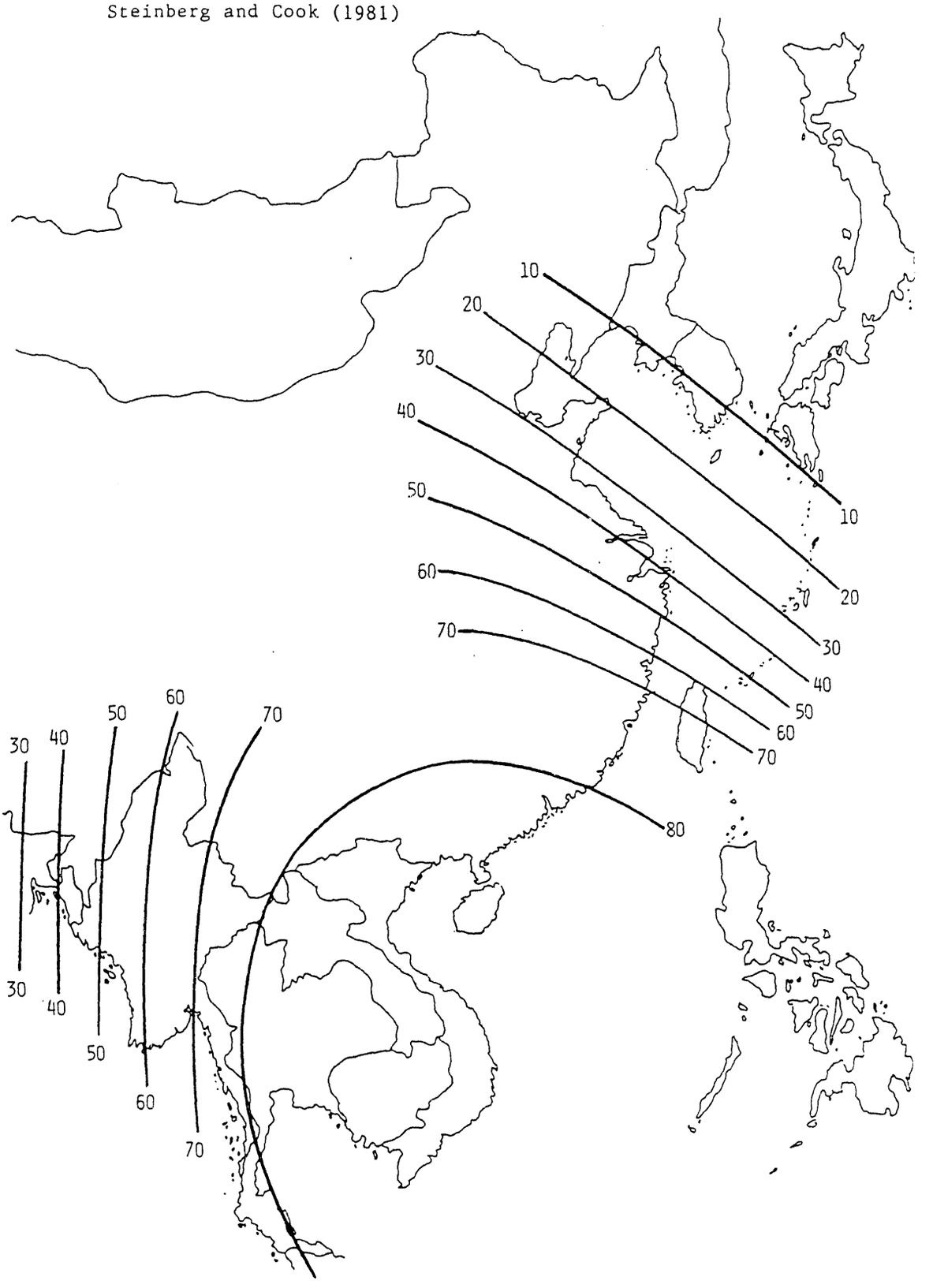


FIGURE 8
DISTRIBUTION OF GM* 3,5,10,11,13,14 IN EUROPE

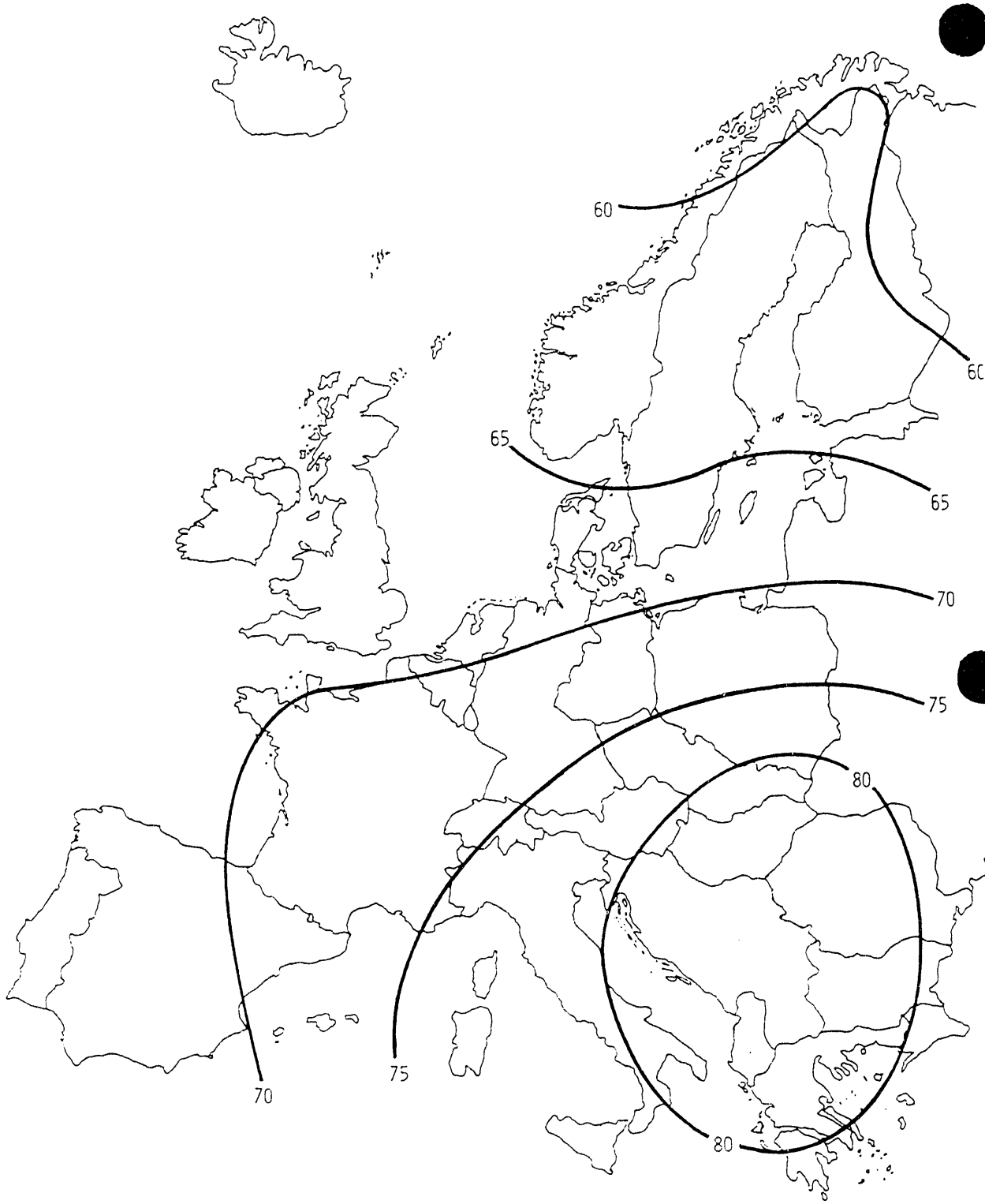


FIGURE 9
*Pvu*II DIGESTS OF HUMAN DNA

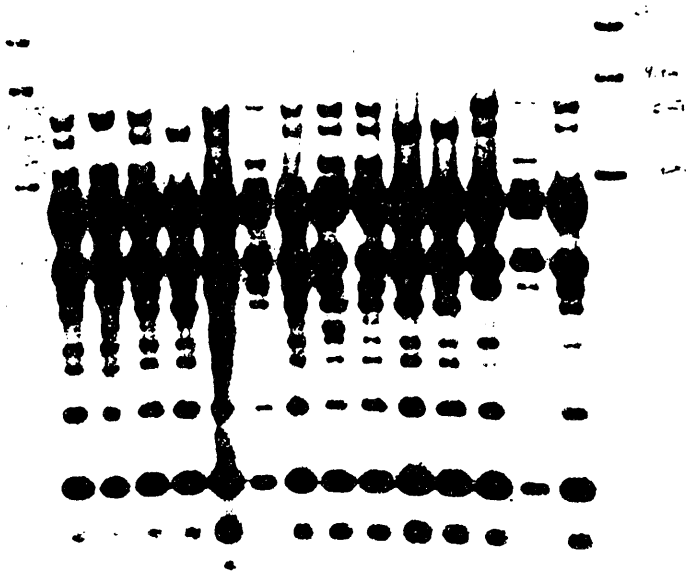


FIGURE 10
KM TYPING BY PCR AND *Acc*I DIGESTION

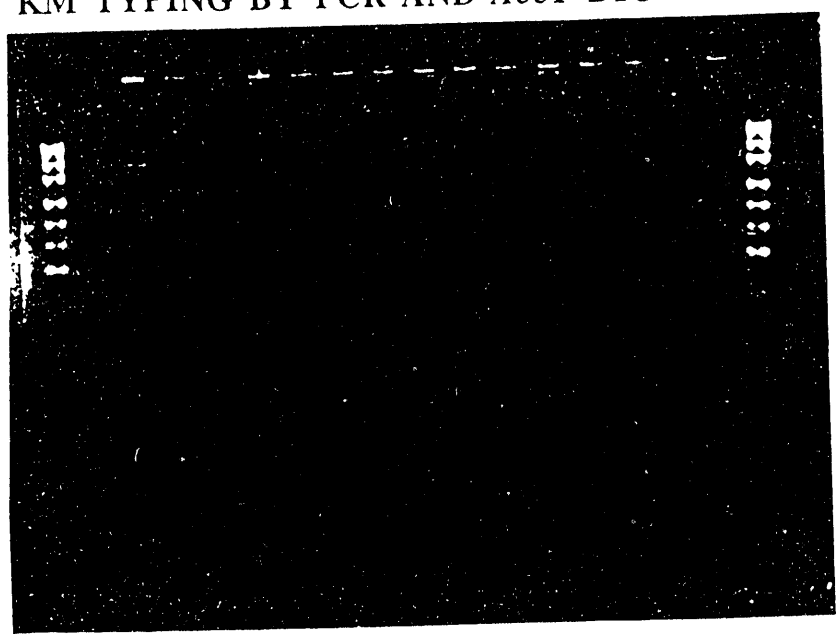


FIGURE 11
KM TYPING BY PCR AND MaeII DIGESTION

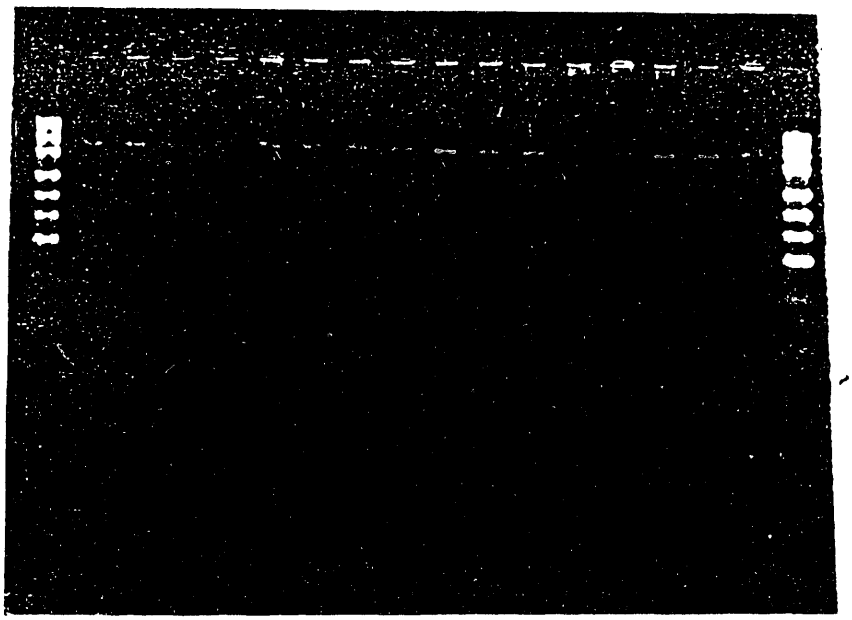
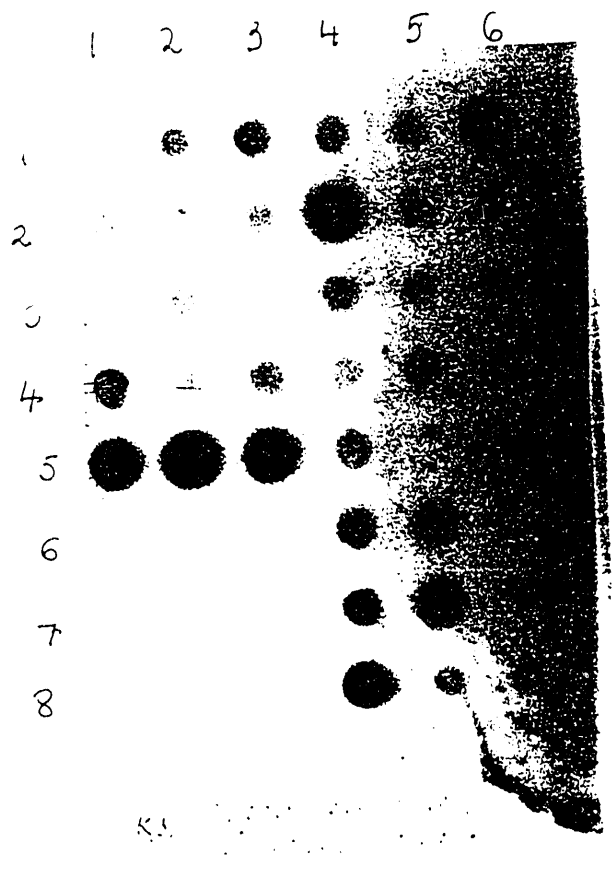
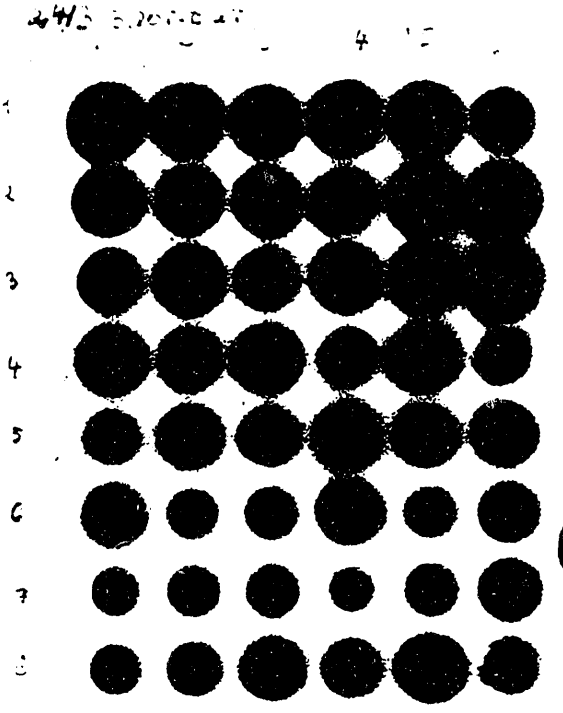


FIGURE 12
KM TYPING BY PCR AND ASO PROBES





Edmond J. Yunis, M.D.

NEW ADVANCES IN THE GENETICS OF MHC

Deyanira Corzo, Marcela Salazar, Juan Yunis, Clarissa Granja and Edmond J. Yunis
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

The genes that regulate the immune response are mapped in the HLA (human leukocyte antigen) region which is located on the short arm of chromosome 6. The Major Histocompatibility Complex (MHC) are closely linked genes of the HLA responsible also for important aspects of immune regulation.

The molecular genetic basis for polymorphisms of HLA class I and HLA class II alleles is due to differences in nucleotide sequences within the coding regions of the individual HLA genes. HLA typing has historically been performed by the standardized microcytotoxicity assay using allospecific alloantisera, rabbit complement, and purified lymphocytes as the target cells. However, use of molecular biology techniques in typing HLA determinants has been a significant advance in Immunogenetics and Transplantation. Specifically, the polymerase chain reaction (PCR) made possible to sequence many alleles of HLA and also to develop simple methods to type alleles or specific sequences shared by a group of alleles. The PCR is a modification of the normal process of DNA replication in which the enzyme polymerase directs the amplification of only a desired fragment of DNA instead of the whole genome. PCR has been the cornerstone for several typing techniques, as it is detailed bellow.

PCR-SSO (sequence specific oligonucleotides). This technique uses the amplification by PCR of the second exon (hypervariable region) of the genes being tested. The amplified product is blotted onto a membrane and hybridized with the number of probes necessary to recognize all the hypervariable regions. With this method, even one nucleotide mismatch will not permit the annealing of the probe specific for an allele. Some probes are specific for one allele and others are specific for a group of alleles.

PCR-SSP (sequence specific primers). In this technique the PCR reaction is directed to selectively amplify only one allele or group of alleles. This is accomplished by designing specific primers with a sequence complementary to that or the allele or group of alleles. Typing results can be obtained simply by examining the presence of amplified products by gel electrophoresis.

PCR-RFLP (restriction fragment length polymorphism). This method uses amplification of the second exon of the genes, and endonuclease digestion able to distinguish the changes in the hypervariable regions within the second exon of the amplified product. Comparison of the fragment patterns with the standard patterns for homozygous and heterozygous individual permits the assignation of the alleles carried by the individual being tested.

Direct sequencing of PCR products. This method is based on the sequencing (determination of the nucleotide structure) of the HLA locus which gives high resolution and detects each one of the nucleotide substitutions not restricted to the ones located in the hypervariable regions. This technique is unlikely to become a routine method due to its cost.

HLA typing with molecular biology techniques allows an accurate assignation of alleles and improve the allograft survival in organ transplants as well as in bone marrow transplants, where it also decreases the incidence of graft versus host disease.

The new advances in the understanding of the role of MHC genes in alloreactivity, the genetics of natural killing, and the genetics of autoimmunity will be discussed.

The Harmony Project's
Harmony Institute for Environmental Compatibility
April 28-30, 1994
Charleston, SC

Report submitted by Dylan Holmes
Medical University of South Carolina
Environmental Hazards Assessment Program

The Environmental Hazards Assessment Program (EHAP) and The Harmony Project of Charleston recently co-sponsored a symposium on environmental compatibility at the College of Charleston's Harry Lightsey Conference Center.

In general, the symposium provided participants with broad-based information categorized by subject. The three-day program attracted participants from grassroots environmental activist groups, builders and developers, scientists, government workers and business executives. The central theme of the conference was effective use of available resources without causing harm to the local community and environment.

The first day of the conference focused on opportunities available to businesses to improve environmental compatibility. Business executives from regional companies provided information on new, environmentally friendly materials and furnishings available to the consumer. Speakers included Ms. Melanie Byrd of the Alumax Corporation, Mr. Rich Reeves of Environmental BioTech of Charleston, and Mr. Russ Perkins of Fenn Vac. Ms. Sue Schweikart of the South Carolina Department of Health and Environmental Control (DHEC) contributed to the discussion by providing insight into state building requirements.

The second day of the conference was devoted to exploring advances in alternative and energy-efficient vehicles. Mr. Robert Ferrel, with the Electric Vehicle Program at York Technical College, described in detail the successful integration of electric vehicles at his institution. According to Mr. Ferrel, the college has expanded on its original U.S. Department of Energy grant to encompass technical training for its students. This discussion was followed by presentations from Ms. Karen Robinson of Electric Power Technology and Mr. Dan Stungis, Design Director for the Trans2 Corporation. Both speakers provided current information on advances in the design and efficiency of electric batteries.

Afternoon sessions of the conference shifted in focus from building and construction to environmentally compatible interior design. Senior Project Designer Ms. Katina Asbell of J.P. Limited of Atlanta, GA, and Mr. John Pourman, President of Highlighters, Inc., discussed new techniques used to increase the efficiency of home energy consumption and interior design. Discussion expanded to include information on "the Greening of the White House" and using nature as the primary source for conditioning.

During the third day of the symposium, the format shifted from presentations to group discussion. The main topic of the third day was environmental justice and securing equitable distribution of environmental risk among all citizens. Discussion was moderated by Dr. Mel Goodwin, director of The Harmony Project, assisted by Ms. Sharon Robles, also of The Harmony Project.

Mr. DeLane Garner of the Southern Organizing Committee for Economic and Social Justice led the discussion. Mr. Garner focused initial conversation on community activism as a way of combating environmental racism. Mr. Garner's comments were tailored to grassroots organizers and community activists in the minority community. He feels these groups often are alienated by the environmental regulatory process. Mr. Garner stressed self-reliance and knowledge as ways to prevent the continued siting of

environmentally hazardous and unwanted projects in minority and impoverished communities. Mr. Garner is currently a research associate at Clark Atlanta University in Georgia. He has extensive hands-on training in regulatory issues, environmental justice and risk assessment.

Supporting data was presented by Mr. Carlton Waterhouse, legal council for the Environmental Protection Agency's Region IV office in Atlanta, GA. Mr. Waterhouse supplemented the information presented by Mr. Garner with a brief background of current environmental regulations. Mr. Waterhouse also facilitated the discussion by clarifying murky regulatory information and answering questions posed by participants. Mr. Waterhouse also recommended direct and indirect pathways community leaders may use to address environmental impact issues in a substantive way.

Mr. Wayne Fanning, representing DHEC, added to the discussion by explaining that agency's role in the environmental regulatory process. Community leaders in attendance appreciated the information Mr. Fanning provided.

The information presented by the three men served as a catalyst for group discussion. Although at times discussion became heated, the information exchange among the group was enlightening. Community persons added a dimension of reality to the hypothetical information discussed by presenting real-life situations occurring in their neighborhoods. Mr. Sanford Lewis, an attorney from Boston, MA, capstoned the data exchange by providing insight into the organization of The Good Neighbor Project for Sustainable Industries in Waverly, MA. The Good Neighbor Project, founded by Mr. Lewis several years ago, supports community efforts at minimizing hazardous environmental impact.

Mr. Lewis and Mr. Garner stressed the need for self-reliance as the cornerstone for environmental equity.

This segment of the symposium was scheduled to conclude at noon. Discussion among group members extended well past the scheduled conclusion. Several of the panelists left by 1 p.m. due to prior engagements; however discussion remained lively and unconstrained.

The Harmony Project selected a variety of well-qualified speakers to participate in this group discussion. Many of the community leaders present expressed gratitude for the opportunity to attend such a forum and were disappointed only in the number of community activists in attendance.

Clues to Unraveling the Association Between Illness and Environmental Exposure

June 3, 1993 Charleston, SC

Presented By:

Environmental Hazards Assessment Program
Agency for Toxic Substances & Disease Registry (ATSDR)
and
Medical University of South Carolina College of Nursing

Report Submitted by Jill C. Tompkins
Medical University of South Carolina
Environmental Hazards Assessment Program

Overview

On June 3, 1994, the Environmental Hazards Assessment Program (EHAP), the Agency for Toxic Substances & Disease Registry (ATSDR) and the Medical University Of South Carolina's College of Nursing sponsored a conference focusing on the association between illness in the community and exposure to environmental hazards. The purposes of the one-day program were:

- To help develop a corps of health care professionals better able to understand the relationship of exposure to hazardous substances and the resulting adverse health effects;
- To understand and promote appropriate intervention; and
- To be prepared with informed responses to community concerns related to environmental exposures.

The Audience

Though the program was directed toward nursing professionals, participants spanned the spectrum of health care, including school nurses, industrial nurses, health educators, professors, medical students, county health officers and environmental quality managers. With 44 in attendance, the conference reached health care givers from areas across South Carolina. (See attached Participant List.)

Welcome & Introduction

The conference began with the customary registration and light breakfast followed by the announcement that the day's pre-planned schedule would not be followed. Nevertheless, events flowed smoothly as coordinators supplied adequate information and direction throughout the day. Welcome and Introductions were given by Lillian Mood, R.N., M.P.H., of the South Carolina Department of Health and Environmental Control (DHEC); Diane Narkunas, M.P.H., of ATSDR; and Glenn Fleming, Ed.D, of EHAP.

Segment I
Basic Concepts of Health Risk Communication
Max Lum, Ed.D., M.P.A. (ATSDR)

Dr. Lum's presentation was both engaging and effective in reaching the program's objective. Dr. Lum focused on the fact that hazardous waste is a primary and growing concern of U.S. citizens because of its location near residential communities and its visible health effects. Yet, risk communication is deficient in many of those communities. The reason behind the deficit is often the lack of purposeful exchange about risks between citizens and health care providers. Without this exchange, there can be no answers.

Dr. Lum provided excellent communication skills information by using actual examples encountered by the ATSDR and the lessons learned from these. An effective communicator, ATSDR has found, is honest, understanding, caring, competent, dedicated and accessible.

Furthermore, a good risk communicator plans his or her messages and materials with strategy, does not belittle the public's concern, and takes the initiative to be proactive within the community. Finally, a good communicator evaluates the impact of the information presented in the situation, accepts feedback, and then takes measures to improve the program. Obviously, this is not an easy task and takes the time and effort of dedicated communicators.

Dr. Lum's presentation concluded with a showing of EPA-issued public service announcements that do not meet the standards of high-quality risk communication. After participants had a chance to critique these, Dr. Lum showed improved segments. It became clear just how important clear and effective communication is.

Video Presentation
Beth Hibbs, R.N., M.P.H. (ATSDR) and
Lynelle Neufer, R.N., M.P.H. (ATSDR)

Following Dr. Lum's presentation, Ms. Hibbs and Ms. Neufer presented a short news segment on a CSI corporation hazardous waste procurement and storage site in North Carolina.

With no safety regulations, fires and explosions ensued. Consequently, workers at this site became gravely ill. The manager of the plant felt no remorse and has since gone into the hazardous waste transportation business. This graphic depiction stunned the audience.

Segment II

Public Health Assessment Process

Lovyst Luker-Howell (DHEC)

Ms. Luker-Howell's presentation gave a detailed step-by-step analysis of the Public Health Assessment Process using a Pickens County National Priority List (NPL/SuperFund) site known as Sangamo Weston/Twelve Mile Creek/Lake Hartwell. The lake was placed on the NPL in February 1990, and the health assessment process then followed. By 1992, the Public Health Assessment was released to the public. Since then, risk communication there has been steadily upgraded as citizens have begun to realize the hazards in their community.

Segment III

Client Evaluation and Intervention

Beth Hibbs, R.N., M.P.H. (ATSDR)

Subtitled "Nursing Assessment and Intervention in Environmental Exposure Concerns," Ms. Hibbs' presentation emphasized nurses becoming involved in the teamwork of community communication.

Nurses are best suited to become involved because of their daily close work with the public, because they are trusted and looked up to in the community, and because they commonly are the first responders in crisis situations.

When a nurse is called upon to make a diagnosis after a client has been exposed to an environmental hazard, he or she must obtain an exposure history, an environmental assessment, a health history, and cultural background before effective care can be given. Ms. Hibbs stressed the importance of excellent communication with an exposed client before preparing a diagnosis. Clearly, risk communication is vital on many levels.

Segment IV

Nursing Evaluation at the Community Level

Lynelle Neufer, R.N., M.P.H. (ATSDR)

Ms. Neufer emphasized the use of federal, state and local resources when assessing an environmental hazard and preparing a toxicological analysis in the community. Ms. Neufer established the four points of a nursing diagnosis pertaining to an environmental hazard: determine the target group, determine the potential for harm, determine the related host and environmental factors, and (finally) establish goals and intervention. She defined the role of nurses in such a situation as needing to assess the exposure, assess the degree of the hazard, and most of all to communicate.

Segment V

Health-Related Activities at Toxic Waste Sites

Patricia Price, D.O. (ATSDR)

Dr. Price's presentation was unique and lively as it used a hypothetical situation of a community facing a lead hazard.

Dr. Price also dealt with the very real problem of lead in actual communities. As people take lead into their bodies through their work environment, paint, stained glass windows, lead shot, lead pipes, some ceramics, and solder, they begin to experience the symptoms of lead poisoning. Mild cases develop fatigue, irritability, muscle ache, lethargy, stomach discomfort and social interaction problems. Moderate cases of lead poisoning result in headaches, vomiting, weight loss and low skeletal growth. Finally, Dr. Price pointed out that though severe cases of lead poisoning are somewhat rare, intense lead exposure can lead to coma, paralysis and a lead line on the gums. She concluded by stressing the need for health care professionals to become familiar with environmental hazards so they can give better treatment.

Closing Statements

To come full circle, Diane Narkunas gave the closing statements, as was fitting since she gave the welcome and introduction. She concentrated on reminding participants of the available environmental health information resources, which include: Hazardous Substance Resources for Consultation, Referral, and Follow

Up; Environmental Health Education Activities for Health Professionals and Communities; ATSDR Environmental Health Education Materials and Information Resources, and the vast array of computerized environmental information resources. Other vital contacts nurses might utilize include: local health departments, the Environmental Protection Agency, Poison Control, toxic substance hotlines, and ATSDR regional representatives.

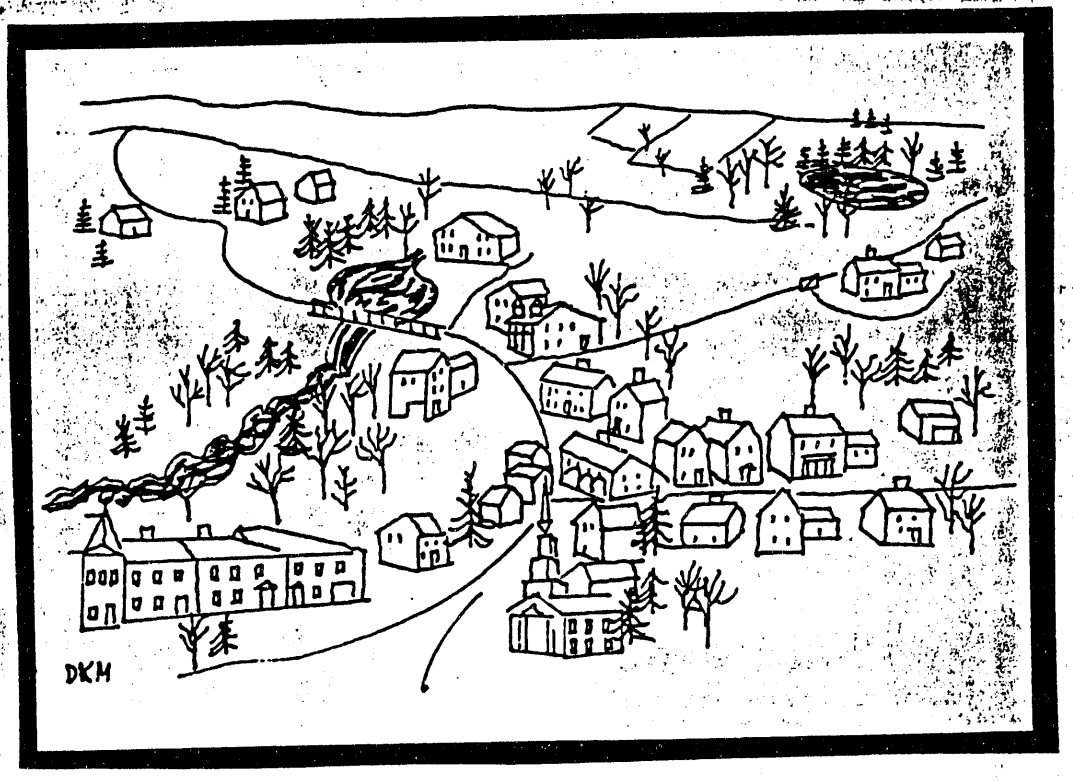
Ms. Narkunas also walked participants through the excellent resources given at the conference which were prepared in a notebook for each participant to take with him or her to use. As there was an overwhelming amount of information given during the conference to retain and use from memory, the notebook was excellent as a take-home resource.

Summary

Though the objectives of the conference seemed a bit ambitious, they were met quite well in the allotted time. Participants seemed thoroughly interested and very receptive to the information being presented. Overall, the day was a success for everyone involved, from the coordinators and funders to the participants themselves. The title fittingly sums up the day's efforts. The word "clues" does imply mystery but also a trail to finding the answer. Perhaps this is the most important first step in effective communication.

A copy of the workbook for this workshop is on file with EHAP Program Information Coordinator Richard Jablonski.

SMALL TOWN ENVIRONMENTAL HEALTH



CROSSROADS OF HUMANITY - ENVIRONMENTAL HAZARDS ASSESSMENT PROGRAM - MEDICAL UNIVERSITY OF SOUTH CAROLINA JUNE 1994

FORWARD

Much appreciation and credit must be given to many dedicated persons from both small towns and public offices who have freely shared their experiences, knowledge, and advice with the author.

Among those deserving appreciation from some wonderful towns are the following:

> Mike Cahill, Bill Hall, Randy Canupp, Van Garner, Ronny Kerr, Bobby Williams, Roland Owens, Bob Rogers, Darrell Adams, Spencer Teffetler, Wesley Brown, Bobby Williams, Marty Wright, Barry Turner, William Wright, Jim Self, Steadman Mears, John Baker, Jeff Cash, Kenney Poole, Timothy Sessions, Chuck Clayton, Lee Rogers, Kieth Mundy, Ken Brisco, Gerry Byers, Kenneth Roberts.

From many public and private offices at the state, national, and federal level appreciation is expressed for the following:

> Tom Moore, Dorothy NcManus, John Hess, Ann Cole, Dr. Wendy Kaye, Gale Alston, Dr. Steven Thacker, Bob Nash, Gary Morgan, Dennis DeWalt, Dr. Michael Silversteen, Sue Andrei, Cdr Garry Crittle, Dr. Max Lum, Dr. Stanley Schuman, Bruce Rosenthal, John Meager. Heidi Kline, John Jones, Don Whitely, Howard Manning, Carol Kocheisen, Mary Giguere, Roland Owens, Tim Bradley, Duane Moore, Don Herd, Doug Williams, Chris Waters, John Hess, David Word, J.I. Palmer. Philip Sheperd, J.B. Howes, Linda Rimer. Christy Russel, Bill Gentry, Andrew Romanet.

Mistakes in fact or interpretation in preparing this brief review are solely those of the author. Comments, corrections, and additions are welcomed. Todd D. Stong, PhD, TEL: (703) 719-9200.

Cover sketch - "Rensselaerville Lake and Ten Mile Creek" by D.K. Martin.

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1.0 EXECUTIVE SUMMARY

The Medical University of South Carolina, under a 5 year grant from the Department of Energy, has instituted the Environmental Hazards Assessment Program (EHAP). From its Crossroads of Humanity Series, EHAP has sought an understanding of environmental health activities in small towns. A product of this series has been the identification of a potential need for developing training and the drafting of "how-to" publications for selected persons in small towns.

The purpose of this study has been to directly evaluate the environmental health support needs of small towns, to determine which are not presently being satisfied, and to identify the various governmental and private organizations for coordination. From this position, recommendations were to be develop for addressing MUSC's best role in behalf of small towns, and what specific products MUSC may consider creating for these towns.

Over 100 telephone interviews were conducted with various national professional organizations, governmental officials at several federal agencies down through state and county offices in turn, and with many individuals serving in small towns, principally in Georgia, North Carolina and South Carolina. From this broad body of knowledge several dozen publications were secured and reviewed for further insight.

Though several federal agencies and a like number of national professional organizations have responsibilities relative to either human health or the environment as related to hazardous materials, little of what they develop has significantly reached to the large number of "small towns." In that 85% of the 39,000 local governments in this country are over populations of less than 10,000, there is just an enormous number of people to reach. Targeting mass, most national programs focus on the top 15% of governments where the majority of the population resides. Simple return on investment judgements often preclude bringing publications or training to the multitude of small, loosely organized, volunteer governments. Consider that over 50% of our country's local governments are with populations less than 1,000. In sum the delivery of anything to small towns is a challenge. This study judged that once a town's population fell below 3,500

persons there no longer were the tax revenues to support any significant staff, especially technical. Fully 90% of the emergency responders in towns of this size are volunteers with an average service of three years.

Realistically, hazardous material incidents are a very small item in most any town. With a chemical, mostly gasoline, tank truck accident once in about three years for the average town, and a significant facility chemical incident being about once a decade in a rural county, interest is relatively low. Local fire departments seldom have any chemical suits because the incidents are so rare and there are not funds to purchase the variety of suits required. Contrary to local belief that most incidents are related to transportation accidents, studies have shown that there are equal numbers in fixed facilities, they just have eluded detection better in the past. With the Right To Know legislation causing holders and producers of hazardous materials to report these to local authorities, more eyes are opening to potential events that may be unobserved within the bowels of a factory or the remoteness of a farmer's field or storage shed.

Potential targets for MUSC support would be town officials, physicians, and emergency response personnel, which includes the emergency medical technicians. Their general needs are for information, planning guidance, and training.

Of these three groups, it is the emergency responders that may have the greatest need for medically related support from an EHAP initiative. Recognizing chemical hazards, knowing the health effects and having a proper understanding on how to decontaminate the victims and fellow responders can be a challenge, especially when the material should not come in contact with water. EMTs may be an especially good group for MUSC to consider, for their training seems to have the least sponsorship, with the Department of Transportation ironically being more the lead than the medical agencies of our federal government. Any attempt by MUSC to provide support to first responders in general deserves careful coordination with a goodly number of organizations that have a similar interest. There is no monopoly and coverage is poor relative to hazardous materials.

Local officials are very seldom (less than 1%) involved in the

response action to a hazardous materials incident. Directives from EPA, FEMA, DOT, and others have fostered the creation of an automatic response network that is centered in the local fire company, and linked by standing committees to the county and the state. The concerns of local officials are more over communication with the populous, gaining sound advice, sensing general liability, and seeking funds for remediation of a significant event that is most likely not to happen in a 5, 10, or 15 year stretch in office.

Physicians appear to have hazardous materials incidents at a lower priority than either of the former two groups for they neither expect an event or are they subject to liability concerns of a public official. They have a very full case load with so many other things, that gaining their attention may be the most challenging. As noted in the recommendations, with the carrot of continuing education credits, a training session at a monthly staff meeting may be the most realistic expectation.

A fourth area for MUSC interest could be its taking a significant role as a focal point for the public, and the de facto coordinator for many small efforts throughout the federal government and with several professional organizations. There is a need for consolidating and organizing information, and providing a better means for its distribution. There are similar needs for coordinating medical training, especially for the non-professional.

At Paragraph 6.0 of this study are listed 17 proposed actions for EHAP consideration. These represent the collective essence of the thoughts and wishes of over 100 persons who in interviews have been asked what is worth an attempt for those in a small town relative to health issues and hazardous materials in our environment. There is mixture of possible publications, training, and advocacy in these 17 offerings.

It is suggested, that no better insight, on the how to do whatever is decided to do, may be had from MUSC's own Dr. Stanley Schuman. He has had an impressive career of dedicated hands on service to rural populations.

2.0 INTRODUCTION/OVERVIEW

2.1 BACKGROUND

The Medical University of South Carolina, under a grant from the Department of Energy is presently completing its second year of a five year program. Their program, entitled, the Environmental Hazards Assessment Program (EHAP), includes several elements, each addressing some aspect of human health as impacted by hazardous substances. The program's Crossroads of Humanity Series has dedicated a series of public forums and exploratory workshops to seeking an understanding of environmental health in small towns. The focus of the series has been on how citizenry may best interact with government, industry and themselves in remediating hazardous substances to human health from their environment. From one workshop a listing of many opportunities for training and the drafting of "how-to" publications emerged. Unknown at that time was what was most needed, who in a small town had those needs, what was not already being addressed by other organizations, and lastly how the MUSC might select its best role. Thus, the subject of this report, a study to address these unknowns was directed.

2.2 PURPOSE

The purposes of this study are many. In the end, it is to provide direction for what training and what creation of written materials should be considered by the EHAP program. Underlying the prescription of these directions has been the need (1) to understand the character of environmental health hazards in small towns; (2) to determine what roles the staff of such a town fulfill; (3) to define what related products are already being provided by higher governmental agencies, industry, and professional organizations; (4) to decide what additional products would meet a need and a demand; and (5) to suggest to the MUSC what actions, with what resources it might choose to make a difference.

4 of 5

2.3 APPROACH

In the pursuit of information for this study, every opportunity was taken to follow routes similar to those that might be taken by citizens and officials from a small town. It was believed that this would evidence most quickly where the information needs were and where the communication break downs might be occurring.

Telephone interviews with both those that would benefit from information in the small towns, and from those that might provide it were of the highest priority. During these interviews references to printed materials were regularly sought. These documents were then secured soon after the interview for further review and leads to other related parties to the problems experienced in small towns.

While seeking interviews and printed materials, a constant mix of higher government offices and small town staff persons was sought. This was done to preclude becoming too enamored with one aspect or the other of the challenges facing small towns.

Although there are a multitude of agencies at the federal level with programs, many overlapping, that touch in some way the issue of environmental health in a small town, they were the easiest to uncover. Their separation of responsibilities was a challenge, and admittedly incomplete in some instances. Professional and other non-governmental organizations were more difficult to identify, but, their spokesmen were well aware of what focus they had for small towns. The approach of state government offices was found to be much more difficult due to missing matches to federal counterpart offices, the wide variance in methods and various titles used to define their conduct of similar programs. Considerably, less funded than either federal or state offices, it was very difficult to identify county level offices that could address their response to environmental health in small towns.

Initially, it was thought that contact with a small town would begin with municipalities of 25,000 or less population. However, at this size town, it was often found that there were ample professionals to address the technical, legal and social issues related to the environment and to fully advise the mayor. In fact, in many cases, a town of this size was staffed better than the

county offices. As this study will explain a downward migration was required until the a town size was identified where the lack of professional services to address environmental health could be examined. Once those lightly staffed towns were located it was soon apparent that the fire chief was the place to begin most discussions on what was taking place relative to hazardous materials incident. In turn, emergency medical staff were sought out when they were not co-located with the fire service.

At the local level a variety of things were sought - type and frequency of experience with health hazards, the existence of other than emergency situations (evolving environmental problems), what parties in the town became involved and how, what training and printed materials/videos were being used, their lessons learned, and referrals to other towns that may have had environmental problems. Also sought were the role of the local emergency planning group and the county as well as any contact with state or federal offices, and lastly what assistance they felt might be in demand in a small town.

2.4 SCOPE

In order to attain some confirmation of sensing over the two months during which information was sought, the effort was focused on states in the Southeast, with a preference for Georgia, North Carolina, and South Carolina. Limited sensing was done in Mississippi, Alabama, and Virginia.

Initially a pure listing of towns with past environmental problems was sought. It became evident soon that neither were there many known incidents in small or large towns, nor were there in general any consolidated listings of past hazards short of the EPA National Priority Lists (NPL). The focus was then placed on towns small enough to not have a technical staff which were sufficiently removed from a neighboring large town or city from which they might readily gain assistance. Approximately 40 towns were selected from state maps based on their population and remoteness.

3.0 ENVIRONMENTAL HEALTH RESPONSES IN SMALL TOWNS

Key issues emerging at the town level early in this study included: when is a town small enough to be limited in addressing its environmental health problems, are there a significant number of problems to be faced, what are those challenges, how are they presently responding, what support is in place, and what do they feel they need.

3.1 WHAT IS THE CRITICAL SIZE TOWN?

WHAT IS A TOWN? Although there are many common denominators in describing states and cities, the variations for towns can be enormous in our country. One municipality with a population of over 800,000 is labeled a town in New York state. With 50 states in the nation there are 50 different ways of defining local governments and their responsibilities. The latter word, responsibilities, can become as important a measure as population in characterizing a town. In the southern states, towns tend to have many more responsibilities for services than municipalities of like size in the northern states which often consolidate services at the county level. Of the 39,000 local governments in this country (counties, cities, towns, and townships) 33,000, 85%, have less than 10,000 persons. In fact 20,000 of the 39,000 have a population of less than 1000.

Because of the very varied characteristics of towns, there seemed to have been few efforts by others that have attempted to address their needs in any collective manner on the topic of environmental health or most any other topic. The National Association of Town and Townships has approximately 13,000 members and a staff of 10, with which it attempts to address the general issues of towns. The association's view of a town is a municipality with mostly part-time staff, often including the mayor. Again, because of the varied nature of towns, they also have seldom attempted the production of aids or guidance for the collective group.

Public Law 102-386, 1992, Small Town Environmental Planning Program, administered by the EPA defines 2500 persons as a small town. EPA's Mobilization Program for the Safe Drinking Water Act of 1986 has focused on small drinking water systems, defined as those serving fewer than 3300 persons.
EPA's Small Community Outreach and Education Program was

established to raise awareness for waste water facilities in towns of less than 10,000 persons, with primary focus on those towns with fewer than 3500 persons.

Yet another consideration may be whether a town is such in name only. That is, does it function with a staff and provide a full range of services like other towns. Across the country, in the last two decades, a number of population clusters have sought incorporation for various purposes, especially to keep tax money at home. For example, sub-division incorporation, "country Clubs," are formed to preclude an adjacent community annexing them to secure tax revenue. They judge that they already have a county tax and don't want to assume another tax from the tax base poor city that might try to annex them. Similarly, some population clusters have become towns on paper in order to be eligible for tax refunds from the state, or from grants for various programs from the state or the federal government. For example in North Carolina, state revenue sharing returns two of the six cents from sales tax to the town that generated it. Many of these hollow town governments contract out services, and thus have very little true staff. Can a town of this nature have an environmental health hazard? It sure can, and its problems may be significantly worse than for even a smaller town which has a real staff.

WHEN IS A TOWN SMALL ENOUGH? At what point do towns begin to have significant problems addressing the challenges of environmental hazard incidents? Based on discussions with towns in the SE part of the nation, it is suggested that once the population base is below 10,000 persons, where the technical depth of the municipal staff begins may often not be an adequate match for understanding and addressing other than well defined, obvious environmental incidents. Response to emergency environmental hazards (e.g. fires, explosions, chemical spills), which is almost totally addressed by local fire departments and Hazmat teams, may become tenuous for towns with less than 2000 persons. Once reaching this level, funding for the smallest of volunteer fire departments ($3,000 -15,000 a year) may not match the available tax base or public funding priorities. Accordingly, emergency response calls are relayed to the next larger town or the county. For the purposes of this study in guiding what size towns to focus staff interviews, 1000 to 5000 persons was selected.

3.2 WHAT IS THE TOWN'S VIEW OF ENVIRONMENTAL HEALTH HAZARDS?

Perspective is of course a function of investment. For a mayor, or other key town official responsible to the town's people, the following list offers some views of responsibilities they assume and the functions they address:

- Focus community involvement
- Assure credibility of completed studies
- Promote communications
- Educate town staff and citizens to regulatory responsibilities
- Direct the efforts of public employees
- Protect and represent the best interests of the town

Does a concern for environmental health hazards appear on the mayor's list of priorities? Normally not, but when it does, it is likely to come right to the top, and present a very unfamiliar challenge for him and every other person that may serve the town. If one matches the number of local governments, 39,000, to the number of environmental health hazards reported annually, it is seen that there is less than one a year.

Newspaper headlines may announce with alarm that there are over 500 chemical accidents a week in this county. Without some perspective this may unduly excite many citizens. That is one such accident for about 500,000 persons, or about one such accident every two years for a town of 2,500 persons. This fits with the frequent estimate by small town fire departments that they have about one good fuel tank truck wreck each three years.

A National Research Council study reports 10,000 to 20,000 truck transportation accidents a year and 1,000 to 1,500 rail accidents each year that involve the release of some hazardous material or threaten to release such. Of this 11,000 to 21,500 accidents about 1,000 are deems consequential, resulting in an average of two injuries each. Of those two injuries, only one was related to the hazardous material. Against the 39,000 governments base, one sees that this equates to about one chance in 40 for one of these significant accidents. In other words that is one injury causing hazardous material incident, with one injured person, each 40 years

on the average for any given government. This relates well with the recollection of towns people that were interviewed that spoke of one event a decade in their county as their estimate.

In that more hazards are likely to be related to larger populated areas, the likelihood for an incident in a small town becomes even less. Telephone interviews with many small towns in the Southeast United States suggest that there may be one transportation related significant spill each three years and perhaps a significant incident at a facility in the county about once a decade.

All of the foregoing is based on reported incidents. Because of long term and in depth regulatory attention to hazardous material being transported, the truth is skewed some towards these types of incidents. In fact, from reported statistics, transportation incidents are said to make up 85% of the whole. However, studies in recent years by the Agency for Toxic Substances and Disease Control, suggest that the majority of incidents may be related to fixed facilities and other non-transportation related sources (e.g. agro-chemicals). Similarly the National Association of Towns and Townships estimates that one half of all chemical releases come from fixed facilities. Statistics are often not generated for incidents that happened with less fanfare inside of industry walls and in a farmer's fields. When a chemical plant explodes or a pesticide warehouse burns the event does come to light and become a statistic, .

From the mayor's vantage point, what you don't know you don't know. To his view, 85% of the incidents are emergencies and transportation related, his concerns are only raised when his resident emergency response organization, the local volunteer fire company can't handle it. He knows that they have more guidance than they can handle from The Department of Transportation, Environmental Protection Agency, the Federal Emergency Management Agency and perhaps a half a dozen more. Further, if the incident is transportation related, there is a high likelihood that there will be a party found to cover the liability (e.g. transporter, manufacturer/producer, recipient/user).

For the other 15% of incidents, which are non-transportation related, fully 14 of that 15 % are again for emergency response actions which will be attended by the local fire company, with

perhaps support from a county or state based Hazmat team. It is only in that less than 1% of the cases, that an environmental health hazard is likely to emerge in some more subtle way that it is not automatically addressed by the fire company. The air may smell worse than usual, the water may take on a bad change in taste, a random water test may show a substance that exceeds standards, or their may be an unexplained increase in some sickness of the citizens, their pets or livestock. When that happens, there is mystery for the mayor. He will first seek help from local resources, most likely not available on the town staff, as noted later in this study. However, if the mystery continues, the mayor will most likely call in the public health officer from the county. If there is some hint of liability on the part of the town or a local business important to the economy, the call to the county may be delayed in hopes a local solution can be found. It is understood once the county is called that soon the state and then the regional EPA could become involved, and the activity will most likely soon escape the town's control.

Returning to the unreported non-transportation environmental health hazard incidents, suppose these were as well known and reported as those associated with truck and train fires and wrecks. Let's speculate that the once in three year incident might become a once a year incident if the full story was known. Will this bring environmental health to a higher priority than taxes, town staffing, traffic, crime, public schools, etc?

In fact, as those non-transportation incidents, that have previously gone unreported, come to light, it is suspected that they will lessen. Through programs like the Right to Known Act which requires those with toxic substances to publicly report them, more light will be placed on potential hazards. The users, the regulators, the town staff, and interested citizens will look harder in a more focused manner. As with trucks and trains transporting chemicals, more visibility led to more care. In sum, it is expected that there will be little increase in the number of incidents which will involve the mayor or his staff, beyond those already addressed by the fire department and the emergency medical service activity. Perhaps there will be an incident to respond to once in two years instead of once in three years. At the county level, the one in ten year incident may grow to a once in five year incident due to the growing better awareness of where the potential

hazards are in our community.

From the town citizen's perspective much depends on their attitude towards risk which may be influenced by the following:

- Knowledge of policies related to environment
- Political values
- Social values
- Confidence that government is monitoring potential hazards
- Distance from a hazardous site
- Level of education (less education = more concern)
  (greater scientific knowledge = greater concern)

The challenge soon can be more communications than technical. How do you establish fact and grade information? How do you communicate risk so as to properly balance fear, wants, and resources?

3.3 WHAT ARE THE ACTUAL CHALLENGES FOR A TOWN?

Given that there are both taskings and help created at higher governmental levels, the need most often at the local level is (1) an awareness of both the tasks and the help, and (2) an understanding of what one should or could do. Among the challenges faced by local officials in addressing environmental health issues are (1) limited time, (2) meager resources, especially staff, and (3) inadequately trained staff.

In a few words, it is simply lack of resources that challenges most small towns in their ability to respond to the very, very few incidents of environmental health hazards that may develop in the community. There are not funds to seek information on conditions that might be hazardous, alone to monitor potential hazards. There are not funds to have any technical staff work for the town. There are not funds to develop even a plan beyond what local talent can contribute. Given the typically enormous expense associated with today's remediation of an environmental hazard, a town hasn't a chance often even to participate, and is thus most likely subject to the will of the final funder.

Experience is also a major challenge, the lack of it for handling environmental hazards. Significant hazardous materials incidents are so infrequent that whole counties go years them. Thus, it is unlikely that a town would have two events in the life time of most of its staff members.

For most small towns, fully 90% of their environmental concerns include: trucks carrying fuel and chemicals, the local dry cleaning plant, chlorine at the water purification plant, underground fuel storage tanks, and pesticide/herbicide storage at the golf course.

3.4 WHAT FACTORS AFFECT THE TOWN'S CHALLENGES?

- Most small town staffs are not experienced in the technical and legal language of environmental health matters. As noted by an EPA staff member, in many cases the regulations are so obtuse that they have to be interpreted by lawyers from the same family that drafted them.

- The volume and varied (multi agency) origin of regulations (state and federal) can be overwhelming.

- There is often much uncertainly on where, when, how, and why to seek assistance when an environmental problem develops.

- What is the availability of resources to coordinate and respond to concerned parties (citizens and regulators), when town staffing levels must be a function of the tax base and in turn the population?

- For response to most environmental health incidents, certainly those of an immediate nature, the focus is on the volunteer fire departments: 80-90 % volunteer, with a 3 year average longevity, making for a difficult and heavy training load (100 hours to put a fireman or EMT man on a truck).

- To field a totally volunteer fire department still requires $4-15k/yr for a small town, with perhaps $4k simply for the liability insurance.

- The cost of fielding a HazMat team, with start up costs exceeding $100k, is often beyond the capability even of many counties.

- Often officials in small towns wear several hats of leadership which can confuse priorities. Accordingly, preparing for infrequent environmental hazards incidents is easily shadowed by higher priorities.

3.5 HOW DOES THE TOWN NORMALLY RESPOND?

Reactions may be a function of perceived liability. Damage caused by a spill from an out of town truck will be paid by others. But, the spill of a truck from a local business could threaten the firm's future and the town's tax base. If the property where the hazard is discovered is on land belonging to the town, it may be handled differently than if discovered on the site of a profitable industry. Does the town want the hazard really remediated or can't they afford the cost?

Potential public reaction becomes another major factor in how a response is mounted. Some of the questions may be, who will be blamed, how will the media respond, how will the citizens react, will outsider activists be attracted, will the jobs of town staff members be in jeopardy

Most often the response depends on how eminent the danger may be. Easily 99% of the known environmental health instances are of the immediate nature rather than those that develop mysteriously over time. Immediate safety, the protection of those in harm's way is the priority. Across the nation, when the hazard is of an immediate nature, it falls to a designated agency, most often the fire department to respond. Local officials typically do not become involved unless the response is beyond the capability of the local fire department. For those events which are not of an immediate nature, something that has been evolving while being monitored, or something of a mystery that seems to be a hazard, it is often judged that there is time to study the problem, to see if it will go away, or simply be ignored until a complaint is raised.

Emergency response is the norm with a well developed federal and

state hierarchy of procedures and standards that are readily acceded to by local officials.

WHAT IS EMERGENCY RESPONSE? A decade ago emergency response was the term applied to a very high percentage of the reactions by the local fire department, mostly to fires, and by the emergency medical service (EMS) staffs, mainly to automobile accidents. But, when the EPA legislated the term Emergency Response for responding to hazardous materials incidents, the term took on a new and very restrictive meaning for many. SARA Title III legislation impacts both EPA and FEMA with its provisions for emergency response. Fire companies still consider fires as emergencies But, Emergency Response has become the term now reserved for those special incidents involving hazardous materials, perhaps 1-3% of their calls. Thus, Emergency Response is now more an at arms length action for local community officials.

Emergency Response is a term that must also now be viewed from FEMA's perspective. FEMA, the offspring of Civil Defense, a bodies that had been formed to respond to disasters, or emergency events that effected significant populations. Although Civil Defense began with nuclear warfare as its focus, FEMA is now oriented on natural disasters - floods, tornados, hurricanes, etc. With the SARA Title III legislation, FEMA has caused each state to create an Emergency Response Commission. In turn Emergency Response Planning committees were established in districts below the state, in counties for the most part. Then at the local level, Local Area Planning Committees were to be established.

The nature of Emergency Response varies by state depending on how the EPA and FEMA directives are carried on independently or merged. For small towns, simply due to the lack of personnel, the directives of FEMA and EPA are normally brought together in one person. That individual is often the Director of the Local Area Planning Committee, and may also be the Fire Chief, Police Chief, Director of Public Works, etc.

OPTIONS FOR EMERGENCY MEDICAL SERVICE Like unto the fire department, the Emergency Medical Service for a local community may be provided by a paid or volunteer force. It may be an integral part of the local fire company or it may be base at a medical

clinic or hospital. Unlike a fire department, there are also for-profit EMS units. State certification of EMS training applies equally to each of these three categories of EMS responders. Relative to MUSC considering programs for providing medically based training to small towns, the EMS organization is a logical target.

3.6 WHAT ASSISTANCE DO SMALL TOWNS DESIRE?

As depicted in the above discussion, fully 90% of the responses to hazardous materials incidents and environmental health hazards are addressed on a routine basis, principally by the local fire department, without any involvement by the mayor or other town staff. Accordingly, comments on what assistance is desired will be separated, with the mayor and what other staff a town may have on the one side, and the fire department with the emergency medical service and the emergency response committee on the other side.

MAYOR AND THOSE DIRECTING A RESPONSE TO AN IDENTIFIED HAZARD: Given the infrequent occurrence of environmental health incidents where the mayor and his staff may act, and their other priorities, what is most needed is an essential understanding, access to a clear and succinct reference book, and a list of experts from the topical area where advice may be required. The mayor's needs may appear as follows:

- Training on the essentials for self and staff. Potential problems and courses of action, regulatory guides, resources to draw upon, etc. (1 day max)

- Training on how to communicate information voids and risk to the public

- Quarterly two page newsletter (new guidance, lessons learned stories, references, etc.)

- Annual update video of 30 minutes length

- Reference notebook listing (1) potential incidents with suggested considerations, health and safety consequences, strategy and courses of action, (2) abstracts of pertinent regulations, (3)

listing of phone numbers for governmental offices with type support noted, and (4) a listing of phone numbers for experts by topics which may be called for advice

- Summary book of that state's pertinent state regulations, in layman's English, similar to that published by the EPA at the federal level

In some ways the needs of a mayor and his staff may also parallel those voiced by public health officers at the county level in a study conducted by the National Association of County Health Officials (NACHO). This study listed the following needs:

- Assessing public concerns
- Alerting the public to potential hazards
- Working with the media
- Responding to public inquiries
- Communicating risk data to the public
- Working with advocacy groups

THOSE RESPONDING DIRECTLY TO EMERGENCIES INVOLVING HAZARDOUS MATERIALS: Although the local fire department may be the center piece in this type response there are many others to be included. Often in this category are: the emergency medical services (frequently a part of the fire department), police who are often first responders, and the emergency operations coordinator from the town or county. The following list suggests some of their needs. Omitted are those things that are most likely beyond the scope of MUSC's consideration, but <u>often cited by those that serve in these many small towns</u> (radio communications, recent vintage fire suits, on-truck hazardous materials computer, relief from liability insurance, and payment of fees for required training):

- Better ways to identify hazardous materials to increase their safety and ability to provide first aid.

- More understanding of health effects to better protect themselves and the victims they rescue

- Quarterly newsletter of two page length providing

medically related topics

- More guidance on decontamination do's and don'ts (e.g. when to not use water to flush a spilled chemical)

- More guidance on how to protect emergency vehicles from loss due to irreversible contamination from transporting a victim incompletely decontaminated

- Consolidated notebook of (1) hotlines and information sources to be called for details on various substances, (2) sources of free and for fee training courses, books, and videos, and (3) abstracts of pertinent regulations

4.0 POTENTIAL ASSISTANCE

Beyond the resources of the town, where might a local official seek assistance in understanding and addressing environmental health issues? The answer to this question has been found most important to understand, for who is doing what for the local government, and what is not or less well addressed that MUSC may wish to consider with its Crossroads Program. Similarly, it became apparent in this study that in order to not duplicate existing programs and to also identify opportunities for collaborative efforts, that MUSC needed to know who was already working what problems.

The Directory of Environmental Sources - EPA/IMSD/91-014, part of the International Environmental Information Exchange Network (INFOTERRA), provides some insight with its 455 listings. Consider that the relative distribution of sources in this collected work may be similar to what one might face in seeking environmental information.

Federal -	152
Non-governmental Organizations -	150
University -	74
State and regional -	24

This prioritization parallels well with what was revealed through contact with many individuals in the Federal government, with professional and private special interests groups, with states and

finally at the county and local level. In short, it seems that the funding and the staff to produce programs, publications, training, and representation of environmental health issues is predominately at the Federal level and with nationally based non-government organizations. On a relative basis there is very little that is provided at the state or county level unless it is funded from a Federal program. The sensing from speaking with state and county representatives is that there are many higher priority issues that are competing for what scarce funds their tax base provides.

4.1 FEDERAL

With the multi-disciplinary nature of environmental science, perhaps it is understandable that when you merge it with health that over a dozen federal agencies become involved one way or the other. For a local official attempting to reach up to the Federal level, many programs can be overlooked, and many that can create confusion due to their overlap. Congress, in its desire to address an issue like environmental health, can easily appear to be using a shot gun. Motivated by wanting to be part of a solution and sometimes for the funding that might come to your organization, many federal agencies have stepped forth with action, often with significant overlap. Fostering this confusion and agency competition for authority over and funding to implement action have been the various committees of Congress which draft our laws. It is not uncommon to arrive at the local level and find that half a dozen federal programs with their attendant regulations apply to your business.

Highly focused federal hot lines are available on many topics. The first challenge is to know that these hot line exist. Then follows the challenge of which hot line if any will help with your problem. The situation seems to be akin to a person with some internal injury having a choice of calling a kidney, lung, or pancreas hotline. The person most likely has no idea in what organ the problem lies. It may be even be for the gall bladder, for which there is no hotline. When your cow comes up sick do you get on the RCRA, CERCLA, Clean Air, Toxics, Clean Water, or Right to Know hotline?

Perhaps the problem is that it really never was meant for small towns or individuals to deal directly with the federal government.

A match between the bureaucracy (organization, mind set, methodology, etc.) of the federal government and a state government, with its own long established bureaucracy has some reasonable chance of connecting. But, without the funding and the numbers of people that make up such a society, the case most often for rural counties and small towns, a match is near impossible. In contrast with the mayor of a large city, few mayors or staff in a small town even attempt to penetrate the maze above them for the time it takes and their need to focus strictly on local issues. The nearest Council of Governments group is most likely the only political like body he seeks some affiliation with to understand what is likely to come down and how he can react.

ENVIRONMENTAL PROTECTION AGENCY (EPA)

With our focus on environmental health hazards one would rightfully look to this federal agency first for support. Yet, its view from the small town is one of a maze with no helpful output and no funding to accomplish required remediations. Towns look to the Regional offices of EPA when they are seeking funding. More so than many other, longer established, federal agencies, the EPA's directions often appear more punitive than supportive. Their orientation has in recent years moved more towards how to cause action other than by court order, how to involve local citizens in local problems, and how to weigh human health risk land use and available tax revenues. Yet most of the information systems and publications produced by the EPA continue to tell one what the laws are and what an industry or local government must do to not be punished. There is very little guidance from EPA relative to environmental health, other than the setting regulatory limits for the permissible levels of a hazardous material. There is no end of hot lines to be called at EPA. But, frustrating to non-technical citizens is the need to somehow express your problem as one with water, air, solid waste, pesticides, a certain class of regulations or similar foreign terms associated with the agency's organizational structure.

Through Emergency Planning and Community Right to Know Act of 1986, handlers and users of a large number of materials that are considered hazardous, are now required to inform the public in writing through various local government offices of what they deal

in. Some interpret this action by EPA as evolving an alternative to regulation - public oversight, thus enlisting citizenry into its police force.

EPA has become a partner with the Federal Emergency Management Agency (FEMA) in establishing Emergency Response Commission/Committees at the state level. The law, called "SARA Title III," or the Emergency Planning and Community Right to Know act," (EPCRA) requires governors to establish State Emergency Response Commissions (SERCs). Each SERC shall divide its state into local emergency planning districts and appoint a Local Emergency Planning Committee (LEPC) for each district." Where certain EPA listed chemicals are present above threshold quantities, they must report to the SERC and the LEPC. Although duplicate guidance has appeared from these agencies in the past, the perception at the local level is that FEMA is now directing that effort. For LEPCs, "the members must consist of representatives of the following groups: elected state and local officials, law enforcement, civil defense, fire fighting, first aid, health, media, community groups and industry." Thus, here is another body that MUSC may wish to associate itself if it chooses to represent some aspect of environmental health to small towns.

Within the last year, EPA has embarked on efforts to address how small towns, with limited resources can address the clean up of hazardous materials. In the spring of this year an EPA committee, under their Small Towns Program, with this mission had their first meeting. Preceding this meeting, EPA published some materials oriented on the small town. Representative of these are, the EPA Small Governments Source Book and the EPA Guide to Federal Environmental Regulations for Small Governments. As per these publications, EPA has establish an office in each of the regional headquarters to be something of a one-stop service for small town governments. Although these offices are designated in the handbooks, calls to those listed phone numbers have resulted in answers that suggest they don't know if they exist. In short, EPA has been directed by the Congress with the Small Towns Act to address their needs. Their focus is, however, aimed at telling small towns about the regulations that apply to them rather than how to remediate environmental problems or better health. The EPA task force, from the Office of Regional Operations and State Local

Relations, initially struggled over developing different rules for small towns (202-260-0456). But, after some time, concluded that even if the small towns had the rules that they would not have the legal and technical resources to understand them. Thus, they felt the need was for "plain language" descriptions of what is needed. The EPA Guide noted above says in its introduction that it is a reference handbook "to help local officials become familiar with requirements ....., to explain a number of these often complex federal regulations in a simple and straight forward manner...." This need for "plain language" is an often cited item when speaking of how to help small towns. The EPA office chief, an experienced, very practical, former city manager from the South, views his office as a broker for small governments. He suggests that there is a "monetary threshold" which dictates whether a small community can make any response to an environmental problem.

Unfortunately, there are many incorporated communities in the country which are not economically viable when it comes to facing environmental remediations. Many of these small communities have incorporated for the simple reason of then being eligible for public grants. They however, have not and do not intend to use their incorporated status to tax their citizens for the cost to provide services, for they have not intended to provide any services.

The Small Town Environmental Planning Program - Public Law 102-386, Oct 6, 1992, 42 USC 5308 directed that EPA establish a program to assist small communities in planning and financing environmental facilities. A small town was defined as one with less than 2500 persons. EPA has established a Small Town Environmental Planning Task Force for which the initial meeting was noted above. This task force will include public interests group representatives. If MUSC wishes to represent some aspect of environmental health to small towns they may wish to seek a place in this EPA planning group. Specifically the task force is to:

- Identify which regulations are difficult for small towns to comply with
- Identify a means for better relationships between EPA and small towns
- Review proposed regulations and suggest changes that will allow small towns to better comply

- Identify a means to promote regionalism of environmental treatment systems and infrastructure serving small towns
- Provide other assistance as appropriate

EPA is to publish a list annually of environmental and public health statutes that apply to small towns. And it is to develop a means to notify small towns of regulations present and future. An Office of the Small Town Ombudsman is to be created. Each EPA regional office will have a small town contact person. Also EPA shall study multi-media permitting for application to small towns. Then within three years of the laws enactment EPA is to report its progress to Congress.

Relative to small towns, the current direction is towards allowing them to operate under less restrictive environmental standards. The driver behind this is the growing existence of Congressionally "unfunded mandates." What is referred to here are the many regulations which are requiring actions for which no funds have been allocated by the government. Interviews at the small town level have revealed instances where EPA's desired action would cost their town ten or more times its annual budget, an impossibility that would simply shut the town down.

1986 Safe Drinking Water Act Amendments require actions that will result in a situation where "90 percent of community water systems that are small or very small will face severe financial, managerial, and technical challenges." (pg 76 EPA RFSG)

Interestingly EPA appears to be moving towards accepting higher levels of hazardous materials in small towns, thus creating a double standard, for those with and without a health tax base. For example, the relax rules on land fills for those taking less than 20 tons/day reflects such thought given to small governments. In that the country generates about 200 mil tons of solid waste a year, the 20 ton/day limit may equate to a town of perhaps 4000-6000 population. If a chemical is hazardous at one level for those that live in urban areas can if be less hazardous for those that live in a small town? It may be the fiscal plight of small towns that will cause EPA to more scientifically and realistically reconsider the agency's hazardous substance mandates.

DEPARTMENT OF TRANSPORTATION (DOT)

This 140,000 person federal agency provides more of the guidance at the local level than might be expected from its title. Although its charter is basically to address road, rail and water shipments it has become a major player in many areas touching on hazardous materials. For example, much of the guidance for emergency medical technicians comes from this agency rather than from the federal health organization that one would expect. Its long title is, the National Highway Traffic Safety Administration, Traffic Safety Program, Office of Enforcement and Emergency Services, Emergency Medical Services (EMS) Division (Coast Guard Commander Garry Criddle, 202-366-5440). This office would like to see EMS included in all planning and training that addresses hazardous materials. The four levels of training that DOT sponsors for emergency medical technicians (EMTs) include:

- First Responder
- EMT basic
- EMT intermediate
- Paramedic

DOT is likewise a major contributor to the creation of training materials for many aspects besides the medical for addressing hazardous materials. Note the Research and Special Programs activity of the Office of Hazardous Materials Initiatives and Training (202-366-4900). DOT Administration provides grants for hazardous materials training in those states that make application for the funding. The state fire marshall is typically the contact point. Similar grants are offered to states for planning their response to hazardous materials incidents. However, DOT does not imposed itself below the state. Since directives from the Reagan era in 1988, Federal agencies don't attempt to direct activities within states.

If there is to be found one book about hazardous materials in a small town, that will most likely be DOT's little orange colored, Emergency Response Guidebook, a Guidebook for First Responders During the Initial Phase of a Hazardous Materials Incident, which fireman, EMTs, police and local officials use as their guide.

Nationally, DOT is the focal point for a multi-agency National Response Center, an emergency network responding to calls 24 hours a day with information and directions for remedial actions.

The Chemical Hazards Response Information System - CHRIS is a Coast Guard (part of DOT) created guide for addressing the response to over 1000 chemical substances. It is both in the form of a book and a computer database (301-321-8440). Many better funded fire departments have adopted this system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)

Health issues related to hazardous materials spills seem to be addressed most strongly from the EPA regulatory perspective, where penalties and litigation are frequently the well publicized outcome. While the health perspective from the HHS, through their Public Health Service, has in contrast more of an advisory and cautionary tone, lacking the comparative teeth of an EPA directive.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE CONTROL

The Division of Health Studies has been collecting information from sites that have experienced an environmental hazard. Presently they are collecting data from 12 states, with a 17 page data record being made for each event. These records document what happened, what materials were involved, how were the people in the area effected, etc. One of the intended uses of this data is to draw from it lessons learned that might be used to assist Local Area Planning Commissions and fire departments. Some of what they are reporting is guidance on what to expect from various chemicals as to human injury potential. They are noting both the more dangerous substances and also the type injuries to be prepared to treat. ATSDR's Case Studies in Environmental Medicine provide specific guidance for addressing health effected by specific chemicals such as lead, mercury, etc.

They found in 80% of the cases that only one major chemical was involved, while many in this field had thought and were training for multiple chemicals in an event. Relative to agricultural chemicals, it was also noted that more injuries come from events

with insecticides than herbicides. One of the major areas of concern is for the first responders who control these events. It seems that they are often the persons most likely to be injured. Accordingly, ATSDR wishes to provide guidance to fire fighters and similar groups. In recent years, a few publications have been created from this data collection. Efforts are underway to produce more publications and to coordinate those efforts with the Division of Education at ATSDR. At this time, data collected by this project is considered sensitive because its release may negatively effect the competitive position of various industries, and various governmental organizations which do not favor its release in a way that identifies a town or a specific industry.

FEDERAL EMERGENCY MANAGEMENT AGENCY (FEMA)

This organization has more impact locally than might be suspected. As an off-shoot of the old Civil Defense Program which had many offices across the nation in small towns, it has inherited those people and their connections with the communities. Although they share with EPA the implementation of the Emergency Response program, it is FEMA that is seen as the actor locally. Frequently the Chairman of the Local Area Planning Committee under the State Emergency Response Committee also has a FEMA hat. Thus, he works closely with the fire department and the EMS group.

The 911 telephone service is another activity linked to FEMA. In large cities the public takes 911 for granted. Many small towns and counties don't have it, for it has a cost, often up to a dollar a month on the monthly phone bill. "Enhanced 911" is an augmented service with the character and the potential for providing small towns access to government organizations and programs that they on their own may not find.

DEPARTMENT OF AGRICULTURE (DOA)

This federal agency impacts small towns in two areas, but that influence is not closely related to a small towns response to an environmental hazardous material incident. The USDA administers a financial assistance program for the construction of water

purification plants, sewage disposal plants and land fills. Additionally, they provide farmers with information on the proper disposal of pesticides, herbicides, and rodenticides. The latter area can be one of significance in rural areas that may otherwise be removed from regular exposure to industrial chemicals.

Representative of the Department's interest in small towns is the Small Community Outreach & Education (SCORE) program which is oriented on assistance relative to waste water treatment facilities with a focus on towns with fewer than 10,000 people, with special focus on those with fewer than 3,500.

Like FEMA the DOA has a local advantage in small towns for they have had representatives on the ground for many years. Thus, should they be so inclined they could be a more effective force than EPA or HHS who you would expect to carry the environmental health banner.

NATIONAL OCEAN AND ATMOSPHERIC ADMINISTRATION (NOAA)

CAMEO (Computer Aided Management of Emergency Operations) is a computerized chemical data base reference system, available on diskettes, provided by the National Safety Council. NOAA developed this data base in conjunction with EPA to allow fire fighters and Hazmat response personnel to have ready access to life-saving information during chemical accident responses. CAMEO, if on a computer with a modem, will also automatically dial CHEMTREC (800-621-7619) in Washington, D.C. for further information and assistance.

DEPARTMENT OF LABOR

OCCUPATIONAL SAFETY & HEALTH AGENCY (OSHA)

There appears to be significant overlap between this agency and EPA. OSHA's Hazard Communications Standard (HCS) or " Worker Right to Know" Rule is a close parallel to EPA's Emergency Planning and Community Right to Know Act (EPCRA). Similarly, with OSHA there is a required reporting of certain chemicals above

thresholds to LEPC, SERC, and the local fire company. The OSHA list of materials is not the same as the EPA list of reportable materials.

Further challenging things for small towns, EPA Toxics Release Inventory (TRI) is being proposed for a doubling of the substances that are regarded as having a potentially adverse effect on people or the environment. Over 300 toxic chemicals would be added, of which 170 are related to pesticides. (320 chemicals now and 313 to be added). Formerly applied only to manufacturing operations, they may now be extended to activities like mining and wholesale distribution.

OSHA has no small towns program like EPA since their jurisdiction only reaches public employees at the federal level, while reaching private industry at all levels. With OSHA's establishment in 1970 there was a division, nearly equal, among the states as to which would allow OSHA enforcement to pass through them to the employers, and those which wish to have a state office perform this function. Among the "State Plan States" are SC, NC, KY, TN, and VA. Examples of states accepting the pass through federal program are GA and AL.

Relative to hazardous materials, OSHA is the developer of safety training that may benefit small towns. Materials labels to include the Material Safety Data Sheets (MSDS) are products that impact what a town does with hazardous materials. It is reported that the MSDSs are an example of an information product which when t reaches the small town level may cause as much harm as it does good. It may be a good example for MUSC to examine when it considers developing materials for small towns. MUSC's Dr. Stanley Schuman has encountered first hand experience in the field with the unwarranted fear confusion and possible mis-information these bring to the citizens of small towns. Difficult to understand technical and legal jargon, combined with questionable reference to chemical tests on animals has at times created more anxiety and grief than good in rural communities.

4.2 PROFESSIONAL ASSOCIATIONS/NON-PROFIT ORGANIZATIONS

Equally numerous as federal offices is a collection of national groups, many of which have an impact on services and information

that reach small towns. Often they are advocates, and more often they are producers of policy, standards, and training used by small town organizations. MUSC may wish to seek affiliation with some of these groups to both collaborate on ventures for small towns, and to seek other types of funding for elements of its EHAP program.

National Association of Regional Councils (NARC)

This organization with its counterparts in each state, Councils of State Governments, is an excellent vehicle for a small town tapping into the political chain without needing to understand how higher governments operate. Council of Governments are associations of city and county officials within a region of a state, which regions have been determined by each state. Their origination stems from the past era when HUD started economic grants to "economic development districts." Planning grants, Economic development Grants, and Job Training Grants meshed with this system of local organizations. The Charleston Council of Governments is the local office in the MUSC area. The Councils are particularly strong and active in the southern USA.

Though their major direction is towards developing policy that will bring states closer, they consider topics of interest to towns. It is a resource where a mayor can go for the big picture, for reference to others that have been down a road he is about to travel, and to find an advocate for a cause he needs to carry to a higher government office. Many mayors are more likely to seek advice first from a local affiliate of this body than from the county or state representative. His questions to the state directly might result in answers he can't live with. To the local Council he can exercise these questions and gain advice.

In North Carolina it was noted there that the Council of State Governments provides advice to individual towns. The chief council noted that they often referred towns to those lawyers that have specific experience in a problem a town may be having. There Resource Guide for Environmental Management, aug 1993 is recommended.

National Association of County Health Officials (NACHO)

With a staff of 15 serving over 3000 members nationally, this group comes closer than any other noted in this study to understanding local environmental health conditions and attitudes. Granted, they do not attempt to penetrate below the county, but much of what they have learned is believed to apply at the town level. Many of the quantified impressions of what is happening at the county level are from their very excellent studies. Heide Kline, their project manager for environmental health, has noted several in depth studies competed and in the works from NACHO. With a staff of 5 for an 8 month period they are soon to complete their Handbook for Local Health Officials Addressing Community Health Concerns. NACHO is very active in drafting standards, and in providing training materials and courses for medical personnel at the county level. They are providing environmental risk communications courses to health officials at state meetings. MUSC may find it very worthwhile to seek collaborative efforts with NACHO. ATSDR is a major funder of NACHO efforts in hazardous materials work. EPA is another significant funder of this organization.

National Fire Protection Association (NFPA)

The NFPA has developed standards that relate to EMTs but they do not address the EMT providing medical care, but rather what he shall wear and how he may protect himself from injury. These NFPA standards have been endorsed by the EPA and OSHA. Standard 472, Standard of professional Competency of Responders to Hazardous Materials Incidents, has application to EMTs. There are 5 categories of certification that may be achieved: 1-Awareness, 2-Operations, 3-Technician, 4-Incident Commander, and 5-Off-Site Special Employee (e.g. a persons from a chemical manufacturer with very specialized capabilities in a single or limited range of chemicals). Standard 473, Competency of EMS Personnel Responding to Hazardous Materials, has two levels. The first is for those EMTs to work in the Cold Zone at a hazardous site and the second is for working in the Warm Zone. Fireman, not EMTs, go into the Hot Zone to retrieved victims which may be contaminated.

As to hazardous materials, the focus of EMT training is for them to be able to recognize what may be a danger to them. For example, if they come on a scene with a methyl ethel cloud, they should go no

further. Their training anticipates that there are too many different chemicals (5000 +) to expect to train an EMT to react to. Thus, the EMT training will most often direct him to call CHEMTRECK for specific guidance on how to handle the chemical or combination of chemicals involved. Recall that the DOT provides guidance for First Responders, EMTs and Paramedic practice. The lack of uniform standards, and the fact that several organizations are generating standards is a concern, one that Mr. Jones is presently working. He believes that there should be an EMS Training director at the state level that prescribes the EMT training. He believes this should be separate from what the state fire academy provides. States currently may select from more than one set of standards for having their EMTs trained. See Appendix D in this study for details on the NFPA.

National Safety Council (NSC)

Produces products of interest to small towns. Early mention was made of the CAMEO portable computer systems used by many larger rural fire departments for accessing information on a wide range of chemicals, and for by modem link reaching the CHEMTRECK system for more information directly from chemical manufacturers.

National Association of Towns and Townships (NATT)

As noted earlier, this organization with less than 15 persons has worked very hard to represent the needs of small towns with the federal government. There publications and network should be of significant interest to MUSC as they move to consider providing materials and services to small towns. Over 10,000 towns belong to this association.

National Association of State and Territorial Officers (NASTO)

This organizations though focused at the state level does address issues and provide materials of interest to small towns. ATSDR is a funder of their efforts.

American Industrial Hygiene Association (AIHA)

Their focus is on industrial operations, labs, procedures for specific hazards, and thus they do not in general prepare materials for local governments. The guidance they provide for industrial facilities - "Emergency Response and Planning" may however be very helpful to small towns. When a mayor is seeking technical advice from one of the town's local industries, the link may be made to the AIHA for hard data.

There are many more national organizations which may merit a examination by MUSC for their products benefit to small towns. The National Association of Local Governments and the National Association of Counties are candidates on this larger list.

4.3 COMMERCIAL/INDUSTRIAL GROUPS

Given the choice of letting federal and state governments set standards for industries involved with producing and handling hazardous materials, many such commercial entities have pooled their resources to created representative organizations to do it themselves. Recognizing the needs for safety standards they have often pioneered in these efforts. They have actively worked with government for an opportunity to police their own ranks rather than have the government attempt it. The result has been a large number of high quality training programs, publications, reference data bases and even computer programs that could be used by the industries they represent, and government at various levels to include the small town. Relative to the environmental health hazards the National Chemical Manufacturers Association (CMA)is an excellent example of a group that represents 100's of chemical industries.

They have sponsored an on-line computer data base with an 800 telephone entrance that is used by a large number of the fire departments, HazMat teams, and Emergency response Committees to reach hard to find chemical information. This system, CHEMTRECK, not only provides access to an enormous database, but is also facilitates direct phone link up with the very technical staff of a plant that has made a chemical. Questions of how to consider strange mixtures of chemicals involved in a fire, a truck or train accident are typically answered via this net work. Whereas EPA may

any of the 50 states has provided a simplified publication comparable to that developed by the Federal EPA for small towns.

Some states like Mississippi and Georgia have established a centralized Hazardous Materials team or teams for the entire state. Others, like South Carolina have both a state level team and many counties with another HazMat team at that level.

The organization of the Emergency Response Committee based on FEMA and EPA guidance has as many forms at the state level as their are states.

In some states the 911 telephone service is controlled statewide, while in others, like South Carolina, it is up to each county to decide what it wants and is willing to buy. A few states have a single number to reach all types of help relative to hazardous materials incidents, while others have a list of numbers depending on whether the hazard is airborne, waterborne, in the soil, a pesticides etc. Neither system is near perfect based on discussions with small towns that must access each. One town noted its call to a central number only resulted in a prolonged argument between various state offices on who should go down to help the town. Fours hours later after calling on the assistance of the local senator and the Lieutenant Governor was the town able to have the state make a move and help.

States environmental offices are in some cases, especially in the south, light on personnel and funds. As a result an ailing town deciding to seek help with an environmental problem is likely to bring it to the attention of the Regional EPA office first where they know they may get funds or the legal muscle to have a responsible industry step up to pay the bill.

In general terms state offices receiving calls with environmental reports number about 3000 a year. The majority of these are inconsequential or repeated calls.
The chief topics are reported to be: handling garbage, expanding water and sewer systems, gasoline spills, leaking underground storage tanks, and transportation accidents involving fuel and chemicals which may present a hazard. Thus, it seems a challenge at and office like this to know when the caller is crying wolf.

Perhaps, that is why some are slow to respond. For the mayor of a small town it appears best to work through his local fire department and the Local Area Planning Committee which has already established its reporting reputation.

States normally neither have a list of towns with environmental problems or a list of those towns which have had an environmental problem addressed in recent time. Thus, it is difficult to identify towns with existing or past problems, other than for those that have been identified by the EPA for inclusion on its National Priorities List (NPL).

Training at the state level relative to environmental hazards is to be found most often associated with a State Fire Academy. Some states have a separate academy for EMTs. Training for Emergency Medical Technicians (EMTs) is accomplished in SC at the technical and community college level. A state board provides an examination which, when passed, certifies one to be an EMT. Every three years they must take refresher training to maintain their certification. The training does not address hazardous material situations to any degree, but rather provides an awareness meant to protect the EMT from entering a situation which could be hazardous to himself. To function on a HazMat team the EMT must take further training which may come through the state Fire Academy. The criteria behind the basic EMT training is as per that prescribed by the federal DOT.

4.5 COUNTY BASED AGENCIES

Seldom are their any environmental offices in sparsely populated or rural counties. But, there is normally a long term commitment to having a health office, though its primary orientation has traditionally been towards sanitation. Hazardous materials are a new challenge, often not well met because of lack of training and compelling arguments that their priorities be on more important problems like food water and general sanitation effecting the health of children. By way of perspective, public health officials communicate with the public relative to hazardous materials about half as frequently as they do for water contamination.

As per, Current Roles and Future Challenges of Local Health

Departments in Environmental Health, May 1992, NACHO, over 80% of local health departments have indicated the following environmental health issues were problems in their community:

- Groundwater contamination (92%)
- Illegal Dumping of waste (91%)
- Private well contamination (90%)
- Recycling (86%)
- Hazardous materials spills/accidental releases (86%)
- Radon (83%)
- Illegal dumping of hazardous waste (82%)
- Surface water contamination
- Asbestos (82%)
- Public water contamination (81%)
- Leaking underground storage tanks (81%)
- Lead contamination (81%)

Obviously many of these problems are interrelated. Some are intermittent and emergency concerns, while others arise as serious problems over a longer period of time. In contrast to the above interests of local health officials, the local emergency response forces concerns, represented primarily by the local fire department and the local area emergency response coordinator, are less numerous. For most smaller communities, over 90% of their activity is devoted to residential fires. They may, about monthly, respond to a gasoline spill, of a few gallons or less, at a local service station. Once every 1-3 years they may experience a truck or train accident involving spilled liquids from ruptured tanks. This mostly involves gasoline from truck accidents, and a wide variety of chemicals from train accidents. At about the same frequency they will encounter gasoline, diesel fuel, or heating oil entering the local sewage pipelines from leaking underground storage tanks. As to a significant and known hazardous material release at an industrial facility they seem to occur on the order of once in a decade when considering an entire rural county.

A NACHO survey of the common issues that local health departments reported as playing a major role, shows hazardous materials spills, as being after many "sanitation" like issues typically related to local health departments.

- Private wells (90%)
- Ground water (88%)
- Illegal dumping (86%)
- Radon (84%)
- Surface water (82%)
- Hazardous materials spills/accidental releases (80%)

When local health departments are asked to focus on what environmental health services they assure their public the following list was developed by NACHO.

- Food protection (92%)
- Nuisance control (88%)
- Sewage treatment (85%)
- Animal/vector control (85%)
- Private well testing (83%)
- Swimming pool inspection (83%)
- Emergency response (80%)

With the increase in recent years of more reporting of environmental hazards to the public the health officers at the county have move to learn more about quicker communication, establishing coordinated positions, and the explaining of risk. Given the variety of federal and state programs that might touch their community, the challenge of knowing what to communicate with whom can be significant. NACHO has done a lot in the past two years to bring risk communications courses to public health officers. It is suggested that MUSC may wish to coordinate its similar efforts with NACHO as MUSC moves further to address the needs of small towns.

4.6 EXISTING LOCAL ASSISTANCE

As discussed earlier, most hazardous incidents of an emergency nature that effect human health in a small town are automatically addressed without a mayor's direction. Only when such an emergency incident can not be quickly addressed by the fire department may a mayor become involved. In fact, often when an incident is being addressed by the local fire department, and further assistance is needed, there is an automatic call to neighboring fire units via

the Local Area Planning Coordinator. Calls to county and state HazMat teams may also be accomplished automatically without involving the mayor.

It is when the unusual and often less dramatic surfacing of possible environmental health problems that the mayor will be alerted by citizens, physicians, his fire department or the media. Of course any such incident becomes a real challenge for gathering information, seeking competent advice, and doing this in a timely manner.

Decisions based on 100% of the information are normally unlikely in the real world. When such information is available, judgements are relatively easy to make and to defend. Leaders, however, are usually designated for those positions where it is expected that direction, judgements, decisions and the like will be a normal requirement, but most often with incomplete and changing information. In to this role, the mayors of small towns find themselves so challenged, with few if any direct staff, especially those with technical experience.

However, even small towns do have some technical resources, often overlooked by governmental bodies who may only through their filter see the lack of their area represented on the town's staff. If immediate safety of the citizenry doesn't force the mayor to appeal to higher governments, he has time to better understand what may be happening and what the potential liabilities may be. He will call upon the local resources with which he works regularly, with whom he has confidence.

FIRE DEPARTMENT: In that 99% of the problems with hazardous materials are normally addressed by his fire department, the mayor may ask them to seek further information from their texts, computer aides, hot lines, and state/national contacts.

LOCAL A/E FIRM'S ENGINEERS: Engineers and technical personnel found in architect and design firms, with which the mayor has dealt regularly in the past for the town's streets, buildings and utilities, are a logical resource with potential information and their own network to other sources.

LOCAL INDUSTRY'S TECHNICAL STAFF: Technical and professional personnel and their linkages to trade organizations may be available in one or more of the local industries. Often they have hazardous material knowledge, references, testing equipment, and computerized resources that would be found in urban fire departments but can not be afforded by the local fire station.

DISTRICT EMERGENCY PLANNING COMMITTEES/LEPCs: The chairman of the local planning committee will most likely have a well developed network of sources of technical information and experience from around the county and possibly the state.

LOCAL AGRICULTURAL EXTENSION AGENT: Should the mayor's dilemma possibly concern fertilizers, pesticides, or rodenticides, this local office may be one logically sought for assistance. These agents are have normally been long established locally and are often viewed as part of the town than an extension of the US Department of Agriculture.

AREA PHYSICIAN: In the establishment of the Local Planning Committee for a town, federal guidance has included health professionals. Many mayors, thus have at least one physician who they regard as being involved in the towns business even though their is most likely no funds for a medical person on the staff.

LOCAL HOSPITAL: Most likely viewed as a county asset, but perhaps not too distant, a mayor may have developed a relationship that will give him access to professional advice here.

AREA JUNIOR COLLEGE: Although typically associated with a city or larger town, a small college may be located in or near a very small town because it is simply at the center of mass of many small towns. The mayor may have access to some technical and professional skills on the staff of such a college.

PUBLIC HEALTH OFFICE: Some towns may have such an office, but most likely this facility is at the county level. In some rural counties that office will be staffed only by a nurse since. Most interviews have suggested that there is typically little knowledge with public health offices at the county, and their is almost an automatic tendency for those offices to quickly elevate a matter to the

higher levels.

Thus, despite the outward appearance that the mayor of a small town has little to no access to technical or professional staff, he may have a well developed network which will be able to discover, interpret and solve the unusual.

5.0 CONCLUSIONS:

(1) Although there may be a regular series of emergencies that impact the health and safety of citizens in a small town, the majority of these are automatically addressed by local police, the fire department and emergency medical service personnel, without involving the mayor.

(2) Hazardous materials incidents are rare in small towns, typically a year or more apart in frequency and most often related to the following:

Trucks and train accidents
Small fuel spills at filling stations (perhaps monthly)
Industrial facility loading and off-loading of chemicals
Pesticides

(3) It is suspected that there are more incidents with fixed facilities than those involving transportation, but the latter are more obvious and more often reported.

(4) Some incidents do not come to public view because they are on commercial property and within compounds that maintain their own fire fighting and hazardous material response personnel. Commercial business with hazardous materials tend to want to care for their hazardous materials without public assistance and monitoring.

(5) Enactment in recent years of Right To Know legislation has provided local governments and citizens with inventories of hazardous materials that may be located within the community, and with Material Safety Data Sheets (MSDS) describing these materials, their handling, and hazardous nature. Unfortunately, in many cases these MSDSs have met the test of lawyers but have created even more mystery and often anxiety for citizens because of their legal and

technical language and questionable reference to animal test data to suggest possible effects on humans.

(6) In small towns the mayor normally does not become involved in an action addressing an environmental hazard unless towns people have to be evacuated, the incident is an evolutionary one with uncertain liability, or funds for remediations are to be sought from a higher governments.

(7) Specific lessons learned from towns that have had environmental problems are difficult to uncover due to the scarcity of examples and the typical non-involvement of elected officials, since the local emergency response forces; fire department, emergency medical service, emergency planning director normally take the action directly from the time of alert.

(8) States seldom maintain a list of towns which have addressed environment hazards in the past, and they normally don't have a list of towns now addressing environmental clean up actions unless they are on EPA's National Priorities List.

(9) Small towns seldom have much direct knowledge of federal programs and assistance due to the lack of understanding the multitude of laws from overlapping agencies, an inability to easily identify the proper titles of a particular office for their particular problem, and due to their state either not having offices to match the federal government, or its having judged that the state's priorities are different than those of the many federal agencies wishing to have their programs adopted locally.

(10) Jurisdiction between evolving environmental organizations and traditional medical organizations is often very confused and subject to wide variations from pace to place.

(11) At the small town level, the impact of varying, and intersecting federal programs is that they tend to coalesce into a single set of actions often with a single individual, the fire chief, public works chief, or the chairman of the Local Area Planning Committee.

(12) Because of many "unfunded mandates" by the Congress there is at present a move a foot to establish less restrictive

environmental standards for small towns.

(13) Many small communities in the US are incorporated for the expressed purpose of becoming eligible for grants from above. They are not functioning as towns with a view to providing community services, and in turn establishing the associated tax base to provide those services. Thus, these communities are towns in name only, and are even less able than traditional towns to respond to community challenges such as environmental hazard.

(14) It is quite challenging to define medically related needs for information and training in small towns because very few officials believe that the frequency of hazardous materials incidents is significant and beyond the knowledge base of the existing responders.

(15) The economics of distributing information and providing training very often result in most program's resources running out once the states and cities have been satisfied. Although 85% of the nations 39,000 governments are over populations of less than 10,000, the majority of the country's population is in the other 15% of governments.

(16) Significant support that reach small towns comes through national professional and trade organizations than through organized federal and state governments.

(17) Presently the majority of medical guidance relative to dealing with health hazards from toxics in the environment is coming from the Department of Transportation, the Agency for Toxic Substances and Disease Registry, and various non-government national organizations.

6.0 PROPOSED ACTIONS FOR EHAP CONSIDERATION

It is suggested that MUSC may choose to become an information producer and conduit for a variety of materials to support small towns in their stewardship of assuring protection from hazardous materials which may injure their citizen's health. This may include publications (hard copy and electronic), training (workshops, lectures and video), and widespread access to collected information via computer bulletin boards and 800 number telephone service. Further it is suggest that MUSC may wish to become a national advocate for environmental health in small towns. The following is listing of 16 specific actions MUSC may wish to consider.

(1) SMALL TOWN OFFICIAL'S ENVIRONMENTAL HEALTH REFERENCE HANDBOOK - For elected or other town officials, develop a single reference that addresses the key information they may value.

(A) Develop a collection of 10-20 potential scenarios involving environmental health that may be faced by a small town. Noted considerations, health and safety consequences and possible course of action. Offer strategy and implementation advice which town officials may consider.

(B) Draft a summary statement with references of the various powers and responsibilities assumed by mayors and their staff with regard to protecting the health of the citizenry from environmental hazards. Seek collaboration and funding from the state attorney general's office.

(C) Create in plain English a collection of summaries of the various pertinent environmental regulations from the state and federal levels.

(D) Compile a directory of experts, on a topical basis, which may be sought for advice. Sub-divide that directory into governmental, academic, association, and commercial sections.

(E) Assemble a descriptive listing of various training and information materials (periodicals, books, videos, courses), that may be of interest to the mayor or his staff.

(F) Prepare a summary description of the top 100 hazardous materials that may be of greatest concern to a small town, along with their potential human health effects. Develop these plain English summaries from existing MSDSs.

(2) WORKSHOP FOR SMALL TOWN MAYORS - Develop a training program with lectures, videos, and exercises that educates a small town mayor and his major staff on the medical aspects of dealing with environmental hazards, where they may seek resources, the lessons learned in other towns, etc. Commence this activity in South Carolina with funding sought from the state. Plan for export to other states in the future. Consider a consolidated video version of this workshop in segments, with possible annual 30 minutes long refreshers.

(3) SMALL TOWN MAYOR'S NEWSLETTER - Distribute quarterly a newsletter to mayors which addresses environmental health issues associated with hazardous materials. Initiate in South Carolina and plan to extend to other states after a year's experience. Seek funding from the state.

(4) HANDBOOK FOR FIRST RESPONDERS TO ENVIRONMENTAL HEALTH INCIDENTS - For fire departments, police and emergency medical service organizations, develop a single reference that addresses the key information they may value.

(A) Assemble and summarize available information which provides guidance on the health effects of various hazardous substances and what first aid is recommended.

(B) Assemble and summarize available information on the proper methods and procedures for decontaminating persons effected by the 300 most common hazardous substances. Give particular attention to those substances that should not be flushed with water.

(C) Assemble a consolidated listing of the hotlines and other sources of information that provide guidance on the health effects

of hazardous materials.

(D) Develop a listing of source for free and low cost publications, videos, and other materials that may support local training.

(E) Draft in plain English summaries of regulations that pertain to responding to hazardous materials incidents and protecting human health.

(5) WORKSHOP FOR FIRST RESPONDERS - Develop a training program with lectures, videos, and exercises that may educate fire chiefs, police, and EMS organizations on the medical aspects of dealing with environmental hazards, where they may seek resources, the lessons learned by other towns, etc. Commence this activity in South Carolina with funding sought from the state. Plan for export to other states in the future.

(6) FIRST RESPONDERS HEALTH NEWSLETTER - Distribute quarterly a newsletter to fire and police chiefs and heads of EMS activities which addresses environmental health issues associated with hazardous materials. Initiate in South Carolina and plan to extend to other states after a years experience. Seek funding from the state.

(7) HOTLINE ADVISORY DIRECTORY - For the many hotlines that now exist across the country at local, state and federal levels; for everything from consumer safety to environmental hazards, to fraud, there is a need to both clearly identify these points of assistance and to understand their coverage. Create a pilot program which produces a directory for South Carolina and the adjacent states. Do this in cooperation with federal and state agencies. Seek federal funding to extend the directory project the next step to other states. Offer an annual update of the directory. Evaluate the potential for placing this information on-line or with a computer bulletin board.

(8) ELECTRONIC BULLETIN BOARD (BB) DEVELOPMENT FOR SMALL TOWNS - Determine what environmental hazard and health bulletin boards of interest exist, define them, assure clarity of access, then establish a BB to link into information sources not touched by the other Bbs. Seek EPA, FEMA, DOT, ATSDR, and NIH sponsorship for this project. Have this BB focused on medically related interests.

(9) PILOT SMALL TOWN MAYORS MEETING - Host a meeting of selected small town officials from South Carolina. Precede that with a meeting of appropriate state and county officials. From these meetings determine the priority needs in the medical service area for a greater understanding and actions relative to hazardous materials and environmental health .

(10) MUSC TO BECOME A NATIONAL FOCAL POINT, A CLEARING HOUSE, GUIDING RESPONSE TO ENVIRONMENTAL HEALTH HAZARDS - Become an agent for bringing to various federal programs which address environmental hazards via their policy, regulatory or training activities, an understanding of the health considerations. Assemble the many participating parties, and become the nationally recognized spokesman. Alternatively, become an active advocate for emergency medical services considerations being included in all planning and training conducted for those that relate to the response at a hazardous materials incident. Coordinate extensively with the ATSDR, NIH, DOT, Association of Occupational and Environmental Clinics, National Environmental Health Association, United States Conference of Local Health Officials, etc. Seek funding from ATSDR, NIH, and HHS.

(11) INSTITUTE AN 800 NUMBER REFERENCE SERVICE - Create an 800 telephone number services that provides information with a medical perspective from the above developed resources, a suite of applicable computer data bases, and access to a computer bulletin board network that will announce a callers needs to a wider audience, and offer to assemble and analyze the responses.

(12) LESSONS LEARNED COMPENDIUM - Seek out 100 towns of less than 10,000 persons which have addressed environmental health problems

from hazardous materials. Collect and summarize their lessons learned. Index the collection by topics that will best suit reference by local officials. Provide in printed and electronic media editions.

(13) ROLE OF HEALTH PROFESSIONALS - Collaborate with a wide range of federal and national non-government organizations in the production of a policy document to define how various health/medical professionals at all levels may become more a part of addressing environmental health as impacted by hazardous materials.

(14) SPONSOR CLINIC STAFF TRAINING - Develop topical presentation to be delivered at the periodic staff meeting in rural hospitals and clinics. This would preferably be done by a medical doctor, and be acceptable for issuing learning credits which the staff has a need to acquire each year.

(15) RISK COMMUNICATIONS FOR ENVIRONMENTAL HEALTH - Develop a training module for on how to communicate to the citizens of a small town the risk related to the effect of environmental hazardous materials to human health. Include in this module assessing public concerns, alerting the public to potential hazards, working with the media, responding to public inquiries, and working with advocacy groups. Consider creation of a companion video which after a one year pilot test in the state may be exported nationally. Seek federal funding. Coordinate with the National Association of County Health Officials.

(16) MATERIAL SAFETY DATA SHEET (MSDS) INTERPRETATIONS FOR THE PUBLIC - The federal government has required industry to produce label-like sheets that are to be place near to or on any container of a substance that may be hazardous. These sheets have been prepared from a perspective that is technically and legally sound, but often very difficult for the hazardous material worker of the public to understand. As a pilot program, develop in plain English versions of these sheets for the 200 most common hazardous

materials. Seek collaboration with ad funding from OSHA.

(17) SMALL TOWN TRAINING GRANTS - Sponsor grants for medical training of officials, physicians, and EMS personnel in small towns relative to hazardous materials and environmental health.

APPENDIX A:

POINTS OF CONTACT & INFORMATION RESOURCES

ENVIRONMENTAL HEALTH HAZARDS FOR SMALL TOWNS

ENVIRONMENTAL PROTECTION AGENCY

RCRA/SUPERFUND Hotline (BAH - Donna)	800-412-9810
Toxic Substances Control Act (TSCA) Hotline	202-554-1404
Clean Water Hotline (Judy Heck)	202-260-5700
Integrated Risk Information System (IRIS) Data base of health risk assessment information on approximately 500 chemicals to help improve risk assessment / risk management activities.	513-569-7245
Office of Regional & State Local Relations (Tom Moore) (Guidebook coord.- Christine Zawlocki)	202-260-4719 202-260-0456 202-260-0244
Emergency Planning and Community Right to Know Program (EPA - Dorothy McManus)	202-260-8606
National Resource Center (NRC) Hotline (EPA/Coast Guard operation) (John Hess - Director)	202-267-2675 202-267-2187
EPA Library	202-260-5922
"EPA Resources for Small Governments" GPO	202-783-3238

Small Community Coordinator Headquarters - (Ann Cole)	202-260-3953
Small Communities Contact - Region 4, Atlanta, Ga. - (Tom Nessmith)	404-347-7109
Region 4 Office - Atlanta, Ga.	404-347-4727 404-347-1033
Health issues (tox) Solomon Pollard & Glen Adams	404-347-3866

DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) PUBLIC HEALTH SERVICE

Agency for Toxic Substances and Disease Registry (ATSDR)

Emergency Hotline	404-639-0615
Emergency Surveillance Data Base (David Barry/Scott Wright/Dr. Wendy Kaye)	404-639-6360
Emergency Response Office (Gale Alston)	404-639-0615

Center For Disease Control

Dr. Steven Thacker - epidemiologist, Legionnaires Disease, toxic cooking in Spain, etc.	404-488-7000

DEPARTMENT OF AGRICULTURE

Rural Communities Clearing House	301-344-3719
Extension Service (Mary Beth)	202-720-3377
Small Communities and Rural Development (Bob Nash - Under Sec)	202-720-4581
(Gary Morgan - Fin Assist Prg)	202-720-9619

FEDERAL EMERGENCY MANAGEMENT AGENCY (FEMA)

State and Local Programs Support Directorate	202-646-3692
Office of Emergency Management, State and Local Support Div. (Dennis DeWalt)	202-646-3318

National Fire Academy (US Fire Administration) Emmitsburg, Md.	301-447-1083
DEPARTMENT OF LABOR	
Occupational Health and Safety Agency (OSHA)	202-219-8148
Office of Policy - Dr. Michael Silversteen (Sue Andrei)	202-219-8021
DEPARTMENT OF TRANSPORTATION	
Emergency Medical Services (Commander Gary Crittle)	202-366-9794
NATIONAL INSTITUTES OF HEALTH	301-496-4000
Intergovernmental Relations Advisory Committee	202-653-6540
NATIONAL PROFESSIONAL ORGANIZATIONS	
National Association of Regional Councils, 1700 K Street NW, Suite 1300, Washington, DC 20006	202-457-0710
National Association of County Health Officials (NACHO) (Nancy Rawding)	202-783-5550
National Association of Towns and Townships (Bruce Rosenthal - sending book, 6 May)	202-737-5200
National Environmental Health Association - Colorado, PC Based	303-756-9090
National Association of County Health Officials (Heidi Kline)	202-783-5550
National Fire Protection Association John Jones - EMS Materials Catalog	617-984-7490 617-984-7483 800-344-3555
National Chemical Manufacturers Association	202-887-1100

CHEMTRECK	
Emergency Hot Line	800-424-9300
Non-Emergency	800-262-8200
Chris Howard Manning - Operations (Statistics)	
National League of Cities	202-626-3000
(Carol Kocheisen - Environmental)	202-626-3020
National Safety Council (Distributes CAMEO Software)	800-621-7619
Association of State and Territorial Health Officials, Produce Training Programs	
Chemical Emergency Preparedness Program Hotline	800-535-0202

OTHER CONTRACTS OUTSIDE SOUTH CAROLINA

Dr. Kenneth Wilcox - Associate with Association of State and Territorial Health Officers, former public health officer at Lansing, Michigan	517-335-8900
Dr. Leslie Haddad - Associate of the College of Emergency Physicians	912-355-8098
Dr. Paul James - Director of the Office of Rural Health, Buffalo University	716-898-5212
North Carolina Environmental Sites (Mary Giguere	919-733-0820

SOUTH CAROLINA STATE OFFICES

Department of Health and Environmental Control	803-734-5360
Information (Pete Saussy)	803-734-4180
	803-734-5000
	803-935-6444
Emergency Response (Spill Reporting - Stan McKinney)	803-253-6488
Emergency Medical Services Certification	803-737-7204
Emergency Preparedness	803-734-8020

VIRGINIA

State Emergency Response (Roland Owens)	804-762-4482 800-468-8892

MISSISSIPPI

Bob Rogers has team for state to respond to emergencies Charles Wilkerson - Brandon local emergency group Carl Carlos - Laurel local emergency group	601-961-5079

ALABAMA

Dr. Brian Hughes	205-613-5347

NORTH CAROLINA

Mary Giguere	919-733-0820

SOUTH CAROLINA

Blufton	Fire Chief (Mike Cahill) 803-757-2800
Croft	803-582-7638
Lockhart	803-427 0800 (Referred to town of Union since no one on duty)
Sheldon	803-846-9221
Spartensburg	County Fire Marshall (Bill Hall) 803-596-3612
Union	Fire Fighting and HazMat Response (Randy Canupp) Emergency Preparedness Director (Van Garner) 803-429-1624 803 429-1622 FAX Emergency Medical Service (Ronny Kerr) 803-427-0351
Walhala	County Seat 803-638-4345 (Referred to Westminster)
Westminster	HazMat Team Chief (Bobby Williams) 803-647-5376

APPENDIX B:

TELEPHONE INTERVIEWS WITH SMALL TOWN REPRESENTATIVES

The below listed towns from three Southeastern United States were considered for interviews.

GEORGIA	
Cedarstown	Landfill, NPL site, VOCs in water 1990
Powersville	Landfill, NPL site, pesticides in water 1983
Blueridge	Gasoline spill that reached sewers in spring 1994, part-time mayor, full-time fire chief
Ashburn	(Turner Co.) three years ago, pesticide, downtown warehouse burned, evacuated town, challenge as to whom to coordinate with and task
Moultry	Town encouraged a new industry in by offering to build a treatment plant for their industrial waste, the plant did not meet regulations and the town incurred a very large cost for making it comply
Lafayette	Chemical company in town had a tank car burn, perception of the hazard by the public was a big problem
Eaptonton	(Putnam Co.) Seed company with building of pesticides which burned, volunteer fire company, local emergency management organization for the county caused nearly three counties to be evacuated for several hours before the extent of the hazard was understood
NORTH CAROLINA	
North Hampton County	Hospital Incinerator
Enfield	Recycling Center

Interviews with small town staff members from representative locations in Georgia, North Carolina and South Carolina follow:

BLUERIDGE, GEORGIA (April 21, 1994)

William Wright - Dir, Emergency Response Team 706-632-2043

He is a past county fire chief who is now responsible for all emergency response activities in town. He is the liaison between the town and the county for various types of support. He is also the director of the 911 service for the town area. This service is a part of the state Emergency Management Agency, under FEMA, which evolved during the Carter administration from the Civil Defense Agency. The town's Emergency Operations Center is co-located with the 911 center. There is an emergency response plan for the town, and they run practice drills to assure that all staff in the town know what to do and know what coordination is required.

In the case of an emergency like a chemical spill, his people would stabilize the situation. To stabilize includes control of crowds, evaluation of people, and calling the state to provide response action. Some might think that the local forces, all volunteers fire departments in this area, should be prepared to do more at the scene. He notes, however, that because of liability issues, it is not desired by these group to have training so that they could respond, because then they would have to respond and face liability issues.

Response guidance is gained principally from the Emergency Response Guide Book from the Dept of Transportation,which directs first response action for working with hazardous materials. The guidebook notes by chemical type what actions are to be taken, such as what area to evacuate. As to other publications being available, he noted that there might be others from government agencies, but that his people received excellent training from a public safety program run by the state.

The local major will become involved in a decision such as evaluating citizens. The town has access to a physician, but it is not expected that he would be called unless there was evidence of people become ill due to a hazardous condition.

If there were possible hazardous material problems in part of town and the specific substance could not be found or identified, it is

In the discussion of both the recent gasoline problems and the long ago border problem the issue of who is responsible for funding the cleanup came across as important. As to the gasoline leak the state had the responsibility and they drew their funds from an account which had contributions from all parties that had underground storage tanks along with the fines that came from each tank that became a violator. For the chemical plant with the leak, Mr. Wright noted that under SARA Title III it was the manufacturer's responsibility.

Newspaper articles on the response can be secured from Victor Morgan at the New Observer, 706-632-2019. **(MAY WANT TO SEE HOW THEY VIEWED THE RESPONSE AND THE ACTION OF THE PARTIES)**

CONFLICT In speaking with the GA. state rep. he presented a picture of over 3000
calls a year over hazards, while the Blueridge emergency response director notes the problem this month as the nearly the first he can remember. Could it be that there is a lot of reporting of smoke but nearly no fire?

TOWN: ANGIER, NC

POPULATION: 2800

CONTACT: Darrell Adams - Fire Department Training Officer
919-639-6234
(Spencer Teffeteler - Fire Chief)

REQUIREMENT: We need more knowledge on the hazardous materials we may be dealing with. We need to know the character of these materials. We need a more time efficient way to train people that have regular jobs. We need something to tell us in an easier manner the procedures for handling various hazardous materials as described in the DOT guide book. As the government imposes stricter and stricter guidelines they are requiring longer and longer amounts of training in more and more subjects. Our people have a very difficult time getting all these hours of training in during the evening after their regular job. It takes a long time to do a 60 hour course, a few hours at a time in the evening, when people need that time for other things. Awareness training only prepares us to look at a hazard from a distance, and Operations training only prepares us for small spill as at filling stations. We need to know how to deal with people that we find exposed when we arrive at the site. We need to know if we try to wash them off with water if will help of make things worse. We need to know something about how to decontaminate exposed persons so that we don't get that material into our emergency medical vehicles and thus possibly cause a big problem there. Sometimes we get training on things, but we have no equipment for that activity. It is like going to hunt a bear without a gun. We could use one of the CAMEO Computer systems (Computer Assisted Mapping Emergency Operations) with its data base of what to do with various chemicals based on the placard numbers on a truck. It is simpler and faster than finding and understanding things in the DOT guide book. CAMEO with its MARPLOT sub-program provides a map of your area, from the Census Bureau, on which the program will draw evacuation boundaries which are easy to understand and communicate to others. Since the CAMEO program costs about $800, it is too expense to buy for this department. One of the in town industries has a CAMEO system that they would like to obtain a free second users license if possible.

TOWN SETTING: A farming community with 3 textile mills and a firm that manufactures fire hose and foam systems.

EMERGENCY RESPONSE PROGRAM: Volunteer fire department with 1 paid employee and 37 volunteers. Training includes: Hazardous Awareness (23 of 38 firemen), Hazardous Operations (17 of 38), Handling Body Fluids, etc. Most training is through local community college. Uses National Fire Protection Association (NFPA) and Occupational Safety and Health Agency (OSHA) publications. Has collected various home videos off of public TV from fireman to use for training volunteer fire department force. Firemen volunteers from the nearby military installation who have had a lot more training can't get it recognized because it was not by state instructors. If a non-specific environmental problem developed, they would call the county public health people.

PAST ENVIRONMENTAL HAZARDS: No local significant hazardous material incidents in memory. Few small quality gasoline spills at service stations each year, treated with adsorbent socks or glandular material. They have responded to large gasoline spills in other nearby towns and have gone as far as 150 miles, mainly because they have a foam cannon because of some affiliation with the firm in their town which manufactures fire fighting foam. The only significant environmental hazard remembered was a chemical leak, perhaps acetone, about 3 years ago in Lillington, NC.

TOWN: WALHALLA, SC

POPULATION: 3500

CONTACT: Fireman, no name given, referred to Westminster
(Bobby Williams - HazMat)
803-638-4345 (803-647-5376)

REQUIREMENT: None offered. Referred all to Westminster station.

TOWN SETTING: Western part of state, a county seat

EMERGENCY RESPONSE ACTIONS: Fire department with 7 paid and 30 volunteers, with EMTs as part of staff. Training received from the Fire Academy in Columbia, which provides instructors to assembly sites in the county.

PAST ENVIRONMENTAL HAZARDS: No comment.

TOWN: WESTMINSTER, SC

POPULATION:

CONTACT: Marty Wright - HazMat team member
803-647-5376

REQUIREMENT: Add medical insight to their training for both. Help the county's put together their HazMat training. (Add to that training a medical perspective.) His wish if there were funds would be for radios to improve communications, and for "full turnout gear", then perhaps some new hoses.

TOWN SETTING:

EMERGENCY RESPONSE ACTIONS: This is the county's HazMat Response Team. They have been in being perhaps over a year, and are still receiving their initial equipment. They have a total of 20 personnel, 12 at the technical trained level. These fireman come as volunteers from the various stations about the county. They cover the county which has 3 major towns. Their role is to "assist" the local fire department. Training comes from the state Fire Academy. Local instructors give classes at various sites in the county. For very serious incidents, the HazMat team at Columbia is called. They are part of the Dept of Health and Environmental Control (DHEC). Publications used include the DOT hazardous materials handbook, the "CRISS" manual (a commercial publication that details chemical properties and especially guidance on decontamination), an EPA hazards manual, and a Southern Railway manual. Duke Nuclear Power, a major industry near, provides them access to many of their hazards books. That industry has its own HazMat team and fire group. He does the pre-fire planning, which involves going to all potential chemical fire sites, and there inventories the materials and draws a plan of where everything is located. For fires where the danger of it spreading are not significant, it may at time be better to allow the hazardous material burn rather than deal with the mess that will that results from soaking the area with water. This may be especially true for pesticide fires where any water that comes off a fire must be collected and treated as a hazardous material.

Decontamination procedures between the local fire department and this HazMat team are still evolving. Casualties must be decontaminated before that are placed in emergency vehicles for they may cause irreversible contamination of the vehicles and the hospital emergency rom on the other end.

PAST ENVIRONMENTAL HAZARDS: No incidents are recalled anywhere in the county for the near 2 years the team has existed. As a straight fireman he does not recall anything significant in the county in the last 10 years. Several years ago a train had a pop-off valve open and there was some confusion until the paper describing the tanks contents could be found. It was harmless. Fires at the textile factories have made for some close calls as chemical storage areas were close to where the fires were controlled. The county did have a fuel truck in the last 10 years burn up. He understood it was let fully burn rather than try to put it out and then have to collect the spilled fuel. One of their more dangerous sites may be an auto engine valve factory which makes its own cyanide. That material can become very dangerous when it comes in contact with water. Some industries want to care for their own fires even though the public fire department may get there faster. At a cotton processing facility, that has many BTB ("built to burn") buildings he has seen losses that might have been saved.

TOWN: **BLUFTON, SC**

POPULATION: 800

CONTACT: Mike Cahill - Fireman (Barry Turner is Fire Marshall)
803-757-2800

REQUIREMENT: Training on the health effects of various hazardous materials. Training for the town employees in the proper handling of hazardous materials they use such as at the water plant or the golf courses. Information for the general public on the hazardous character of chemicals about their homes and work place.

TOWN SETTING: The town is less than a mile square, but this station covers 240 sq mi of territory. They have 14 paid and 30 volunteers in the fire company. There is no industry in or near the town. The hazards in their area include chlorine stored at the water plant, and pesticides and fertilizers stored at golf courses. HazMat protection comes from a team under the county. There is one major chemical firm in the county. The HazMat team is directed by the Emergency Response Committee through the Local Emergency Planning Committee, which has a Funding Committee with business and industry representatives on it. Each business that has hazardous materials places $100-200 into a fund each year to help pay for the operations of the HazMat team.

EMERGENCY RESPONSE ACTIONS: Those that are first responders, fireman and police receive level 1 training and those with the HazMat team receive a level 2 training. The HazMat team does the decontamination of any victims at the site. It is the responsibility of the local fire department to decontaminate the members of the HazMat team that come to assist them on a hazardous incident. Training, sponsored by the state, is accomplished at various stations about the county at different times during the year. They use the DOT Emergency Response Guide Book (1/2" thick) which tells of hazard placards, how volatile a material may be and how to handle that chemical material. They don't have a CRISS book. They also use the Hazardous Materials Emergency Response book from the National Fire Protection Association (NFPA). The NFPA is made up of over 50,000 fire chiefs and engineers. They set

the standards for everything from the training to the trucks to the hose and clothing to building standards that are fire safe. For the situation of a non-emergency environmental problem of unknown character it is expected that the major would call DHEC at the state and perhaps the EPA. The mayor would only become involved if a major part of the town had to be evacuated and/or emergency funds had to be sought from the county or above. The fire company does carry a liability insurance policy for its staff's actions, but it has limits. He has known of a town that was sued to the point that it broke them.

PAST ENVIRONMENTAL HAZARDS: Nothing significant can be recalled for the last 10 years. They have had truck accidents over time but none with hazardous chemicals. To the north in Sheldon they have a chemical plant that has had some minor leaks, spills, and fires.

TOWN: **UNION, SC** (Had called Lockhart, but they were closed and referred the call to Union)

POPULATION: 10,000

CONTACT: Randy Canupp - Fireman and HazMat team member - 803-
Van Garner - Emergency Preparedness Director for the county
803-429-1624
Ronny Kerr - Emergency Medical Service 803-427-0351

REQUIREMENT:

TOWN SETTING: Lockhart with a population of less than 100 has no fire department, all calls are referred to Union

APPENDIX C: HAZMAT TRAINING AND THE NATIONAL FIRE ACADEMY

BACKGROUND:

The National Fire Academy, a Federal Emergency Management Agency (FEMA) subordinate facility under the United State fire Administration, located in Emmitsburg, Maryland is the major US originator of HAZMAT training materials. The other producers of training materials for hazardous materials are the Department of Transportation, American Management Association, selected states, and a few corporations. Most of the curriculum materials generated at locations other than the National Fire Academy often contain facts and figures from the National Fire Academy materials. The National Fire Academy is federally funded at approximately $11 million per year and manages grant monies of $11.2 million.

The Grant monies pay for developing training curricula, pay the cost of professional instructors and allow professional and volunteer fire and rescue personnel alike to obtain the materials free. The local departments order the materials using Federal grant money obtained through their state to pay all costs. When Grant money is used the Grants require a class size of at least twenty. The materials are produced to reach the 2.5 million US fire and rescue personnel.

The National Fire Academy estimates that their are 500,000 professional and 2 million volunteer fire and rescue personnel within the 50 states and 4 territories. Turnover is very high. Career turnover for both the volunteer and professional is averaged at 3 years. Turnover and material upgrade creates a continuing training requirement. This is a major problem.

DISCUSSION:

There is training material available. But many small communities, especially those staffed by volunteers, are often unaware of the training available or cannot afford it or hesitant to obtain Grant money to get the material and training free.

FREE TRAINING EXISTS

Many communities don't know how to get the free training materials produced by the National Fire Academy. The problem is that communities are baffled on how to get Federal Grants to pay for the material. Many see the Grant program as red tape. The purpose of the Grant program is to provide an audit trail of paperwork that insures only qualified personnel receive the materials for actual instruction.

GRANT MONEY

Even without the Grant money the course materials are relatively cheap, costing several hundred dollars a course for the instructor manual and materials, supporting visual training aids and student course materials. The academy course materials are field tested across the nation for at least 2 years, validated, refined, modified, improved, and reviewed. The materials can be assumed to be accurate and effective. However, it is often very difficult for the local volunteer departments to raise the funds for the training material.

The Grant programs require 20 people to receive the training at a time. This is especially difficult in rural situations with volunteers. It is difficult to get 20 volunteers together. Some rural areas just cannot get 20 volunteers together on any given evening.

The courses provided are legislated to be given to groups of 20 or more to cover the cost of the instructor that administers the materials. The courses can be given anywhere but there is now a trend for using the community college setting for the volunteers and professionals.

TWO LEVELS OF COURSES

There are two levels of courses for the fire and rescue personnel. The first level is the "awareness level" and the second is the "operational level". These courses may be further divided into a technician level course and a command level course. Certification of the individuals taking the training is totally voluntary. In the past individuals refused becoming certified

because of possible litigation problems. This was reportedly a significant issue with volunteers.

PROFESSIONAL STANDARDS

All of the National Fire Academy course materials meet the National Professional Qualifications System Standards. The National Fire Academy was established to "to advance the professional developmental of fire service personnel and of other persons engaged in fire prevention and control activities". The Academy also offers two week in-resident college level courses for anyone with substantial involvement in fire prevention and emergency management activities.

All of the material produced by the National Fire Agency meet Occupational Safety and Health Agency (OSHA) regulations and standards and the American Council of Education quality standards.

SMALL COMMUNITIES ARE NOT AWARE

Small communities are often totally unaware of the National Fire Academy and its efforts to build training curricula. The Academy materials flow to all fifty states and territories and may or may not go any further. In discussing this issue a National Fire Academy Assistant Superintendent stated "State directors have been known to control the information concerning the Grants to carefully control their own power base".

SUMMARY:

Small community volunteer fire departments are reportedly often not aware to hazardous training materials that may be obtained from the National Fire Academy. Others may be aware of the training availability but cannot afford it, or cannot get enough people together to apply for Grant money for professional instruction, or cannot get through the paperwork involved. Many small community leaders are hesitant when working through a State Agency to get a Federal Grant.

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Akron, OH 44320
216/ 873-2442

This journal contains scientific articles and technical reports relating to detection, evaluation and control of occupational, environmental and radiological health hazards, as well as air pollution problems. It also includes articles about human and animal toxicology, product safety and applicable subjects covering the broad field of occupational health. Special articles include industrial hygiene summaries, new products and literature, book reviews and professional news.

Frequency: Monthly; Price: $100 per year.

American Journal of Epidemiology
Society for Epidemiologic Research
American Journal of Epidemiology
2007 E. Monument Street
Baltimore, MD 21205
301/ 955-3441

This is the principal journal for the reporting of epidemiologic studies in the U.S.

Frequency: Biweekly; Price: $95 for individuals, $190 for institutions.

American Journal of Public Health
American Public Health Association
1015 Fifteenth Street, N.W.
Washington, DC 20005
202/ 789-5600

The American Public Health Association publishes a medical journal that contains the current news and events of the public health field.

Frequency: Monthly; Price: $100 for individuals, $160 for institutions.

Analytical Toxicology, Journal of
Preston Publications, Inc.
P.O. Box 48312, 7800 Merrimac
Niles, IL 60714
708/ 965-0566

The *Journal of Analytical Toxicology* serves toxicologists, chemical researchers and educators engaged in clinical, industrial and forensic toxicology. It includes articles in industrial toxicology, environmental pollution and pharmaceuticals.

Frequency: 7 copies per year; Price: $210 per year.

Archives of Environmental Health
Heldref Publications
1319 18th St., N.W.
Washington, DC 20036
202/ 296-6267

This publication provides objective documentation on the effects of environmental agents on human health. Its articles describe research from epidemiology, toxicology, biostatistics, and biochemistry

Frequency: Bimonthly; Price: $90 per year.

ChemEcology
Chemical Manufacturers Association
2501 M St. N.W.
Washington, DC 20037
202/ 887-1100

This newsletter of the Chemical Manufacturers Association contains articles on the ways in which the chemical industry is responding to environmental issues and regulations.

Frequency: Monthly; Price: Free.

Chemical Information Manual
Government Institutes, Inc.
4 Research Place, Suite 200
Rockville, MD 20850
301/ 921-2355

This manual is used by compliance safety and health officers as a reference for sampling chemicals during industrial hygiene inspections. It contains a wide variety of useful data on over 1,200 chemical substances, including the proper identification by OSHA's IMIS No., CAS No., DOT No., etc., OSHA's permissible exposure limit, action level, or ceiling value, carcinogenic status, major health effects, and sampling and analysis techniques for each chemical listed.

Frequency: Irregular; Price: $69.

Chemical Substances Control
Bureau of National Affairs, Inc.
9435 Key West Avenue
Rockville, MD 20850
800/ 372-1033

This publication is a guidance on regulatory compliance and management of chemicals--from premanufacture through disposal. It provides explanations of how to comply with the laws and regulations governing chemicals--including toxic and hazardous chemicals, pesticides, and other substances. This manual explains the requirements for premanufacture and use, testing, reporting and recordkeeping, labeling and packaging, transporting, and disposal of chemicals.

Frequency: Biweekly; Price: $610 per year.

Chemical Times & Trends
Chemical Specialities Manufacturers Association
P.O. Box 1897
Lawrence, KS 66044
800/ 627-0629

Chemical Times & Trends contains articles which report on trends and developments in the manufacturing and selling of industrial, household and personal care products. Articles discuss legal, environmental and regulatory issues important to the chemical specialities industry.

Frequency: Quarterly; Price: $27 per year.

Community and Worker Right-To-Know News
Thompson Publishing Group
1725 North Salisbury Blvd.
Salisbury, MD 21801
800/ 879-3169

This newsletter reports on chemical disclosure requirements, emergency response programs, hazard communication and industrial liability.

Frequency: Bimonthly; Price: $379 per year.

Ecological Society of America Bulletin
Business Office of the Ecological Society of America
Center of Environmental Studies
Arizona State University
Tempe, AZ 85287-3211
602/ 965-3000

The *Ecological Society of America Bulletin* is a professional publication for individuals interested in the study of living things in relation to their environments.

Frequency: Quarterly; Price: $25 for members.

Ecology
Business Office of the Ecological Society of America
Center of Environmental Studies
Arizona State University
Tempe, AZ 85287-3211
602/ 965-3000

Ecology is a scientific journal which contains information on the study of living things in their environment.

Frequency: 8 issues; Price: $180 per year, for members.

Emergency Preparedness News
Business Publishers, Inc.
951 Pershing Drive
Silver Spring, MD 20910
301/ 587-6300

This newsletter is written especially for those public officials, business executives,and non-profit sector managers charged with preparing for and dealing with natural and man-made disasters. It looks at resources and strategies for coping with crises, and emergency response management techniques and technologies.

Frequency: Biweekly; Price: $261.04 per year.

Environmental Action
Environmental Action
6930 Carroll Avenue, Suite 600
Takoma Park, MD 20912
301/ 891-1100

This publication examines the impact of human beings and industry on environment and the effect of industry on humans. Specific interests in this publication are toxicants, energy, and health.

Frequency: Quarterly; Price: $25 per year.

Environmental Contamination and Toxicology, Bulletin of
Springer-Verlag New York, Inc.
175 Fifth Avenue
New York, NY 10010
212/ 460-1500

The *Bulletin of Environmental Contamination and Toxicology* is a publication of significant advances and discoveries in the air, soil, water and food contamination and pollution. It also contains information dealing with methodology and toxicants in the environment.

Frequency: Monthly; Price: $338 per year

Environmental Education, The Journal of
Heldref Publications
1319 18th St., N.W.
Washington, DC 20036
202/ 296-6267

This journal is written by educators for other educators for teaching methods and skills to keep them informed on environmental issues. Features case studies of relevant projects, evaluations of new research & discussion of public policy & philosophy.

Frequency: Quarterly; Price: $53 per year; this publication can be purchased at discount through the North American Association for Environmental Education.

Environmental Ethics
Environmental Ethics
Department of Philosophy
University of North Texas
P.O. Box 13496
Denton, TX 76203-3496
817/ 565-2727

The *Environmental Ethics* journal is dedicated to philosophical aspects of environmental problems and is intended as a forum for diverse interests and attitudes to bring together philosophy traditions with the technological world.

Frequency: Quarterly; Price: $18 per year for individuals, $36 for libraries.

Environmental Executive Directory
Carroll Publishing Company
1058 Thomas Jefferson Street, N.W.
Washington, DC 20007-3832
202/ 333-8620

The *Environmental Executive Directory* is a comprehensive listing of who's who of the top environmental executives. The directory provides coverage of 2,500 top companies; 300 top business and professional associations; 600 environmental service and consulting firms; the top 500 legislative, executive and state officials with environmental responsibilities; 200 law firms with environmental practices; 200 public interest groups and non-profit organizations; 100 international groups with environmental interests, and the top 200 environmental columnists, reporters, newsletters and publications.

Price: $165.

Environmental Health, Journal of
National Environmental Health Association
720 South Colorado Boulevard, South Tower,Suite 970
Denver, CO 80222
303/ 756-9090

This journal covers all phases of environmental health. The articles are original and deal with scientific, educational and general phases of environmental sanitation. It examines food, radiation, recreation, water supplies, stream pollution, vector control, air pollution, housing, hospitals, schools and accident prevention.

Frequency: 10 issues per year; Price: $45 per year for nonmembers.

Environmental Health Perspectives
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709
919/ 541-3406

This environmental publication is currently for people with knowledge and background in the science fields. It is a scientific journal in technical language which contains proceedings from scientific conferences and issues on target organisms and environmental assaults. In the near future, however, the journal will be expanded to include environmental news, commentary, and environmental calendar of events, etc. Its scope will also become less technical in nature in the future.

Frequency: 6-8 issues per year, but soon to be monthly. Price: $52 per year.

Environmental History Review
American Society for Environmental History
Center for Technical Studies
New Jersey Institute of Technology
Newark, NJ 07102
201/ 596-3291

Environmental History Review is an international journal about human ecology as seen through history and the humanities. This publication encourages dialogue between the disciplines to strengthen them and bring them to a better understanding of the relationships between the environment and humans.

Frequency: Quarterly; Price: $24 per year for individuals; $30 for institutions.

Environmental Physician, The
American Academy of Environmental Medicine
Box 16106
Denver, CO 80216
303/ 622-9755

AAEM publishes a newsletter which features articles on environmental medicine and includes numerous abstracts.

Frequency: Quarterly; Price: $30 per year.

Environmental Progress
American Institute of Chemical Engineers
345 East 47th Street
New York, NY 10017
212/ 705-7663

Environmental Progress is a publication of the American Institute of Chemical Engineers which deals with multifaceted aspects of the pollution problem. It provides thorough coverage of abatement, control, and containment of effluents and emissions within compliance standards. This publication includes papers which cover all aspects of environment pollution including water, air, liquid and solid wastes, and reports on the progress and technological advances vital to the environmental engineer.

Frequency: Quarterly; Price: $125 per year.

Environmental Science and Health, Journal of
Part A: Environmental Science and Engineering
Marcel Dekker, Inc.
P.O. Box 5005
Cimarron Road
Monticello, NY 12701
914/ 796-1919

This journal emphasizes engineering innovations, control systems, and the chemical fate of pollutants and pollution levels and sources.

Frequency: Eight times a year; Price: $465 per year.

Environmental Science and Health, Journal of
Part B: Pesticides, Food Contaminants, and Agricultural Wastes
Marcel Dekker, Inc.
P.O. Box 5005
Cimarron Road
Monticello, NY 12701
914/ 796-1919

This journal provides a common focal point for scientific papers from all pertinent disciplines concerning pesticides, food contaminants (natural and additives) and agricultural wastes.

Frequency: 6 issues; Price: $395 per year.

Environmental Science and Health, Journal of
Part C: Environmental Carcinogenesis Reviews
Marcel Dekker, Inc.
P.O. Box 5005
Cimarron Road
Monticello, NY 12701
914/ 796-1919

This publication provides multidisciplinary, concise, critical reviews covering all aspects of chemical carcinogens in the environment.

Frequency: Two times a year; Price: $210 per year.

Environmental Science & Technology
American Chemical Society
1155 16th Street, N.W.
Washington, DC 20036
202/ 872-4600
800/ 333-9511

Environmental Science & Technology, edited for chemists and engineers involved with environmental quality; contains research articles on all aspects of environmental chemistry and commentary on the scientific aspects of environmental management.

Frequency: Monthly; Price: $444.

Farm Chemicals Magazine
Meister Publishing Company
37733 Euclid Avenue
Willoughby, OH 44094
216/ 942-2000

This magazine contains articles and staff research reports on the production, marketing and application of fertilizers and crop protection chemicals. Material is for the fertilizer bulk blender, fluid mixer, pesticide/fertilizer dealer, aerial applicator and ground rig operator to improve operations and to sell products and services. Emphasis is on government regulations new product registrations, crop clearances and applications.

Frequency: Monthly; Price: $20 per year.

Hazardous Materials Control
Hazardous Materials Control Research Institute
7237 Hanover Parkway
Greenbelt, MD 20770
301/ 982-9500

This magazine provides technical information, introduces innovations, and provides articles from leaders in the hazardous materials field.

Frequency: Bimonthly; Price: $18 per year.

HazMat Transport News
Business Publishers, Inc.
951 Pershing Drive
Silver Spring, MD 20910
301/ 587-6300

This publication is designed to keep up with new laws and regulations at federal, state, and local levels on toxic and hazardous substances. First hand coverage of congressional regulatory and investigative agency actions plus the latest news from around the country is covered in this newsletter.

Frequency: Biweekly; Price: $345.54 per year.

Industrial Hygiene News
Rimbach Publishing, Inc.
8650 Babcock Boulevard
Pittsburgh, PA 15237
412/ 364-5366
800/ 245-3182

Industrial Hygiene News provides product information for persons responsible for industrial hygiene and toxicology functions. It includes new products, new literature, book reviews, and product briefs.

Frequency: Bimonthly; Price: Free.

Industrial Safety & Hygiene News
Chilton Company
One Chilton Way
Radnor, PA 19089
215/ 964-4055

This publication serves persons responsible for purchasing and using safety, industrial hygiene, fire protection, security and emergency first aid equipment and related services. It includes reports on equipment selection and usage, state-of-the-art developments, product applications, research and standards.

Frequency: Monthly; Price: $42 per year, free to qualified people in field.

Management of World Wastes
Communications Channels, Inc.
6255 Barfield Road
Atlanta, GA 30328
404/ 256-9800

The *Management of World Wastes* serves persons involved in the management of solid, liquid and hazardous wastes. Articles describe and analyze public and private sector operations including how wastes are stored, collected, handled, transferred, hauled, incinerated, recycled and processed for the recovery of materials and energy. News stories examine developments in technology, labor and law.

Frequency: Monthly; Price: $45 per year.

Merck Index, The
Merck and Company, Inc.
P.O. Box 2000
Rahway, NJ 07065
800/ 999-3633

This book is an exhaustive, one-volume encyclopedia of more than 10,000 chemicals, drugs and biological substances. An internationally recognized reference work, it is widely used by chemists, pharmacists, toxicologists, physicians, biologists, chemical engineers, and many other professionals. The Index includes illustrated chemical descriptions, tables and charts, a cross index and a wealth of other information in over 2000 pages.

Price: $35.

National Emergency Training Guide
Emergency Response Institute
4537 Foxhall Drive, NE
Olympia, WA 98516
206/491-7785

This loose-leaf publication covers the topics of search and rescue; emergency preparedness education; emergency management strategies and information; emergency response, disaster research; it provides information about publications, new products, videos, training manuals, new techniques, courses and seminars, and disaster research.

Frequency: Every two years; Price: $30.

National Environmental Training Association Newsletter
National Environmental Training Association
2930 E. Camelback Road
Phoenix, AZ 85016
602/ 956-6099

The *NETA Newsletter* contains articles and information about environmental training programs and training materials. It also carries current employment information.

Frequency: Bimonthly; Price: Free with membership, $15 for nonmembers.

NCLEHA Newsletter
National Conference of Local Environmental Health Administrators
John O.Tironi
2809 Maywood Dr.
Port Huron, MI 48060
313/ 987-5306

This publication promotes efficient and effective local environmental health programs.

Frequency: Two to four times a year; Price: Free to members.

Occupational Medicine, Journal of
Williams & Wilkens
P.O. Box 64380
Baltimore, MD 21264
800/ 638-6423

The *Journal of Occuational Medicine* is concerned with the maintenance and improvement of the health of workers. It is intended for physicians engaged full time in the field of occupational medicine.

Frequency: Monthly; Price: $115 per year for institutions, $84 for individuals.

Occupational Safety & Health
Stevens Publishing Corporation
P.O. Box 7573
Waco, TX 76714
817/ 776-9000

This publication includes news about occupational health and safety; articles of an instructional, technical or scientific nature; and regular departments devoted to cost containment, legal developments and review of literature. It serves as a communication vehicle for occupational physicians and nurses, industrial hygienists and safety professionals.

Frequency: Monthly; Price: $36 per year.

Occupational Safety and Health Reporter
Bureau of National Affairs
9435 Key West Avenue
Rockville, MD 20850
800/ 372-1033

This loose-leaf information service reports on the progress of standards-from OSHA through the enforcement process-of OSHA's right-to-know standards and requirements, federal safety and health standards, regulations and policies, state and federal programs, enforcement efforts, research and labor relations.

Frequency: Weekly; Price: $940 per year.

Pesticide & Toxic Chemical News
Food Chemical News, Inc.
1101 Pennsylvania Avenue, S.E.
Washington, DC 20003
202/ 544-1980

This newsletter contains up-to-date analysis in areas of: the Toxic Substances Control Act, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the Resource Conservation and Recovery Act, Superfund, and Government regulations affecting chemical production, transportation, disposal and occupational health.

Frequency: Weekly; Price: $715 per year.

Spill Control Association of America News Brief
Spill Control Association of America
400 Renaissance Center, Suite 1900
Detroit, MI 48243
313/ 567-0500

SCAA News Brief is a membership newsletter for companies and individuals concerned with cleaning up spills of hazardous products and manufacturers of specialized products for spill control and clean up, and protection of individuals.

Frequency: Quarterly; Price: Free with membership.

State Environment Report
Business Publishers, Inc.
951 Pershing Drive
Silver Spring, MD 20910
301/ 587-6300

This report covers state legislative and regulatory initiatives and their prospective impact on operations dealing with toxic substances and hazardous wastes. It contains information on hazardous waste siting prohibitions, transportation routing requirements, public and worker right-to-know laws, and state regulations requirements.

Frequency: Weekly; Price: $431.50 per year.

Toxicology and Environmental Health, Journal of
Taylor & Francis Group
1900 Frost Road, Suite 101
Bristol, PA 19007
800/ 821-8312

The *Journal of Toxicology and Environmental Health* emphasizes toxicological effects of natural and anthropogenics, and the effects of environmental pollutions and their actions on organisms and in vitro systems. The topics in this journal include: carcinogenesis, mutagenesis, teratogenology, neurotoxicity, environmental factors affecting health, and review papers on broad subjects.

Frequency: 12 issues, 3 volumes; Price: $649 per year.

United States Government Manual
Superintendent of Documents
U.S. Government Printing Office
Washington, DC 20402-9371
202/ 783-3238

This annual single volume contains data about each government agency and its subdivisions. Names of officials, history of the creation of an agency and its functions, addresses and phone numbers of field offices are also included. This is a useful document for anyone dealing with the federal government. Also available from Government Institutes, Inc. at 301/ 921-2300.

Waste Age
National Solid Waste Management Association
1730 Rhode Island Avenue, N.W.
Washington, DC 20036
202/ 861-0708

This magazine is for persons interested in the control and use of solid, hazardous, chemical, and liquid wastes. Attention is given to new methods and new applications of existing techiques and this publication features reports of the latest political, economic, social and technical developments covering collecting, handling, hauling, transferring, incineration, burying, recycling or otherwise dealing with wastes. It includes industrial as well as institutional, commercial, private, municipal and county waste problems.

Frequency: Monthly; Price: $35 per year for nonmembers.

The National Association of Environmental Professionals

19th Annual Conference & Exposition

"Global Strategies for Environmental Issues"

Report submitted by:

Cathi Bare, Public Information Specialist
Dylan Holmes, Research Associate
Sylvia Rivers, Special Events Coordinator

New Orleans, Louisiana
June 12-15, 1994

National Association of Environmental Professionals

19th Annual Conference and Exposition
New Orleans, Louisiana

Report submitted by Cathi Bare, Public Information Specialist, EHAP

Introduction

With the Crossroads of Humanity Series moving from hypothetical situations to real situations and from national forums to community meetings, it is important that the outreach staff become proficient in the management of community involvement, public meetings and process/government regulations. I feel that the National Association of Environmental Professionals (NAEP) 19th Annual Conference and Exposition really gave those in attendance insight on the aforementioned matters. We were exposed to a variety of techniques on resolving public controversy, use of facilitators in public meetings, the physicians' roles in environmental risk assessment, briefing on the NEPA process, an overview of the Savannah River Site, and lowering risk panic by effective communication from an engineer's perspective. All topics that relate to our work with EHAP.

I think it is important that I mention the exposure and recognition EHAP was granted and obtained during the NAEP conference. First of all, the three video tapes were part of the conference and view during the environmental cinema. In addition, abstracts of each of the videos were included in the printed program as well as posters in the exhibit hall. Also, during a plenary session (approx. 300 people), EHAP was mentioned by the president of NAEP Gary Kelman in reference to the work the organization is doing with the Department of Environmental Health Science. Also, Dr. Hugh McKinnon, a senior executive medical officer in the EPA, mentioned his work on Jan Semple's advisory committee to full session.

There were three sessions that I found especially pertinent to EHAP activities and have included those in this report. For information on other sessions, please see Appendix i.

Pre-Conference Seminar 2
How to Prevent and Resolve Public Controversy

Presenter: Desmond Connor, PhD, consulting sociologist and president of Connor Development Services Ltd. of Victoria, B.C.

Dr. Connor's 3-hour workshop concentrated on a specific type of public meeting -- the public open house -- as well as touched on variety of different techniques to resolve public controversy.

The room was set up with about six people per table. At the beginning of the session we were asked to list what we wanted to get out of the session, then discuss these with those around us. Following, participants at each table addressed their concerns, and these were then recorded on easels in front of the room (similar to those used in COH workshops). The facilitator did not allow the same thing to be recorded twice!!! Once everyone voiced their expectations, the large sheets of paper were hung on the wall and we were asked to walk around the room and make our individual top six expectations. Dr. Connor then went ahead with the rest of the seminar. In the end, he tallied the results of the rankings, to find most of us wanted the same things. He felt this was a good way to allow everyone to voice their concerns, then realize that they are not alone, and that many others have the same feelings.

I have enclosed notes that I jotted down during the workshop. These were things that I thought were very important and directly related to EHAP concerns. For details on the seminar please see Dr. Connor's "How-to guide," Appendix iii.

Seminar Abstract: *Often it is a vociferous minority opposition which springs up over environmental issues and derails sound projects. Dr. Connor will five you a greater understanding of the changing social, economic and political climate, and why people resist change. Learn a strategy to activate the silent majority to balance the vocal minority, and eight techniques to implement this strategy. Dr. Connor specializes in the design and management of public involvement programs for corporations an governmental agencies seeking public acceptance of new policies, programs and projects.*

- Get information to participants first
- Let the public get to know each other and find out where they stand (this was in reference to the opening activity)
- Gather a social profile as a starting point: voting patterns, homeowners/renters etc. This info. may be obtained from the planning office.
- Determine open house format vs. community meeting
- Use posters and large graphics
- Put participant views in writing (i.e.. large easels and paper)
- It's advisable to have a community meeting training workshop for presenters, facilitators and staff prior to the event.
- Use local print services for printing brochures.
- Rank alternative solutions
- Special care goes to outreach efforts
- High-end graphics look like decision has been made. Keep things modest.
- In certain instances, an open house followed by a public meeting, might be beneficial. People may feel more comfortable with one-on-one contact, and may find answers directly, instead of standing up at a public meeting.
- You need a post-meeting news release -- people need to know they've been heard.
- Who should be at the open house: Policy people, project managers and science.
- Dr. Connor recommended the book When I Say No, I Feel Guilty.
- Use local libraries to display information about the project.
- Don't forget about: Public Involvement, Public Relations and Public Sector Marketing.

I feel we can learn and utilize a lot from Dr. Connor's seminar. With the open house format, I think people would feel accommodated and that the clients really aren't such bad guys after all. I

would especially like to utilize many of Connor's techniques for the Crossroads efforts in Blackville, SC.

Use of Facilitated Meetings in the NEPA Process

Presenters: *Dorothy D. Letts, Center for Alternative Dispute Resolution, Judiciary State of Hawaii; Honolulu, HI, and John B. Goody, Belt Collins, Honolulu, HI*

Workshop Abstract: *This short course is an interactive presentation on the conduct of public meetings within the NEPA process using professional facilitation and/or facilitation techniques.*

This course will discuss both the advantages and disadvantages of using facilitators during public scoping meetings and draft EIS hearings, how to build form one meeting to the next, and the necessary planning to organize and conduct successful meetings under circumstances that meet NEPA criteria.

NEPA requires that at certain points in the EIS preparation process the general public be encourages to participate. Failure to satisfy the criteria and legal precedent may result in an inadequate EIS. It is the most contentious projects, those most likely to be challenged, and most difficult to make positive and effective. It is in these circumstances that professional facilitation can help meet your meeting objectives.

the fundamental principal is that the "Process" of conducting the meeting must be neutral and separated from the "content" or substance of the meeting. Thus, the meeting may be jointly owned and perceived to be fair by participants of all viewpoints when managed by an independent party. This allows project proponents and the EIS study team to focus on substance. There are numerous planning factors involved in making the meeting work.

This course will show you how to avoid becoming a target, and how to make public meetings work for you in meeting your NEPA obligations.

Again, I have included notes taken during the workshop. For details please see Appendix iv.

NEPA Meeting
Information Giving and Gathering

- Scoping-giving
  - Purpose and need
  - Alternatives
  - Potential impacts
- Scoping-gathering
  - Issues and concerns to be studied and addressed
- DEIS-giving
  - Alternatives
  - Impacts
  - Mitigation
- DEIS-gathering
  - Additional areas not adequately covered
  - Disagreements with findings
  - Significant impacts

Separate process and content of meeting

- Facilitator: Advantages
  - Neutral facilitator frees you to listen
  - Fairness
  - Efficiency
  - Capture information
  - Vehicle for feedback
  - Removes you as target

- Facilitator: Disadvantages
  - Takes more time to prepare
  - Perceived loss of control
  - Cost
  - Unbiased facilitator

- Meeting Planning
  - Purpose: define exactly why having meeting and what you expect to get out of it
  - Timing: when does Federal Register come out?
  - Location of meeting
  - How meeting room is set up
  - Agenda: How much time for presentation vs. comments
  - Record
  - What things is the facilitator responsible for?
  - Mind set of team: positive attitude not just holding this meeting because law says I do

- Traits
  - People will avoid making decisions
  - Self-interest
  - A situation rarely resolved till distrust is eliminated
  - No resolution until voluntary participation
  - Mostly people don't' like begin told what to do
  - People will keep agreements they help formulate
  - No settlement without doubt
  - People are more important than disputes

- Setting up the Meeting
  - Purpose
  - Scope
  - Identify context and stakeholders
  - Establish the desired outcomes and topics for the meeting
  - Establish who needs to attend and key roles and functions
  - Identify how decision will be made
    - Record of decisions
    - Permitting agency
    - Political process
  - Establish detailed agenda including topic process steps and timing
  - Design room set up, check out room
  - Prepare and locate handouts, signs, graphics and visual aides

- Honor 3 minute limit: courtesy to friends and neighbors/ not the rules. (i.e. you're not going to save the base at my meeting)

- Do you really need a court reporter record???--Large news print and easels -- very acceptable

- Presenters sit in audience: do not give them targets -- stand up and answer questions and sit back down
  Don't "them against us"

- Goal: Accepted document, no litigation

- Stakeholders
  Affected by a decision: agencies, parties who are impacted
  Can implement decision
  Can block decision

- Phone surveys, one-on-one /face-to-face prior to meeting

- Send invitations to stakeholders: stress the importance of their input

- Decision Making
  Gather input
  Gather top alternatives
  Inform agency and decision makers
  Don't hide process

- Adequate time for agenda
- Do scope at night
- Must have start time and end time
- Set time limits
- Easy access

- Facilitator's Role
  Establish presentation factors
  Present and clarify format

- Recorder Role
  Creates visual record
  Writes down group members ideas using their own words
  Remains neutral
  Tries not to paraphrase

- Group Memory
  Provides visual record
  Helps groups focus
  Accepts and legitimizes participants' statements
  Provides instant feedback
  Prevents repetition
  depersonalizes ideas
  Frees group from note taking
  Aides accountability
  Low cost and easy
  Provides minutes

- Group Member Role
  Contribute ideas
  Listen to other ideas
  State concerns openly

Conclusions Drawn and EHAP Utilization:

This guy would make a great panelist for the physician meeting. Again, he reiterated what has been said by our own people re. the role of the physician in risk communication.

Lowering Risk Panic by Effective Communication Part II

Risk Communication is an Emerging Democracy: The Hungarian Electricity Board Plant Sitting Project

Presenter: Ray Germann, Environmental Resources Management Inc. (ERM), Exton, PA
Workshop Abstract

In the midst of privatization of Hungary's government-owned properties, the Hungarian Electricity Board began upgrading several power plants during 1992. The project, made possible by a grant for the World Bank, included environmental feasibility studies at three plants as well as an environmental risk communication program. The risk communication program was designed to help affected parties to understand the true health and environmental risks posed by the project and to gather and incorporate public input into the siting process. The ultimate goal was to allow the siting project to proceed without opposition, intervention or delay.

ERM was retained to perform the environmental assessments and to conduct the risk communication programs. This presentation focuses on the performance of these programs and logistical and cultural challenges of conducting such programs in areas where government and national identity is in a state of flux.

It describes the methods used to perform risk communication in a country still adapting to democracy. It also relates the challenges faced by the project team in identifying and dealing with new political leaders and non-governmental organizations and in eliciting input form communities unaccustomed to involvement in environmental projects.

The result of the program was an intricate network of community and government representatives at the local, regional and national levels. This network functioned as an information-sharing vehicle which allowed all affected parties to better understand the relative health risks with the benefits of the project and to demonstrate the need to accept and acknowledge diverse interests and agendas.

Notes:

- Project objectives: Perform environmental feasibility studies for power plant upgrade
- Incorporate public opinion into the study process

Public Challenges

- Identify appropriate public audiences
- Educate audience on to best participate in process
- Deal with diverse and conflicting organizations and communities
- Decipher true agendas and motivations

Three-step Process

- Assessment -- Info. gathering
- Planning -- Info. processing and strategy development

- Implementation -- Outreach activities

Assessment Findings
- Public groups were diverse, disorganized and fragmented
- Local and regional governmental in a state of flux
- Non-government organizations (NGOs) power opinion leaders
- Participation by individual citizens limited

Planning Tenets
- Need to reach all audiences simultaneously
- Communications held in an open forum (no small group meetings)
- Substantial education on how to participate
- Special emphasis on demonstrating effectiveness of public input

Implementation Activities
- Fact Sheets
- Meetings with Environmental Authorities
- Strong follow-up

Conclusions
- Public desire to participation
- Priorities similar to North America
- Similar communication tools (public meeting., fact sheets, briefing)
- Basic concepts that work well here work there as well
- Clear information
- Full disclosure
- Responsive to concerns
- Acting on concerns
- Follow up

Conclusions Drawn and EHAP Utilization:

The gist of this presentation was that Western techniques could be used for European community involvement or an "international symposium." I was also impressed that this was presented by an engineer. It goes to show that the importance of outreach is being recognized by a variety of disciplines.

Environmental Racism, Justice & Equity Problems: Technology Based solutions

Presentor: *Dr. David Padgett, Austin Peay State University, Clarksville, TN.*

Dr. David Padgett is currently Professor of Geography at Austin State University. In recent years he has devoted a large amount of time to developing and refining environmental equity issues as they pertain to geography.

Dr. Padgett focuses on three key issues in addressing current environmental equity problems.

1. Providing scientific-based conflict resolution and investigation to move beyond unfounded emotion-based protest tactics.
2. Discussion of environmental professionals' role in the growing environmental equity movement by reviewing current events.
3. focusing upon long-reaching legal, economic and social aspects of environmental inequity.

Following Robin Cole may not have been the ideal situation for Dr. Padgett. Although much of his information was accurate, a great deal of it had already been presented by Ms. Cole. Instead of emphasising on that part of the presentation, Dr. Padgett instead detailed his work dealing with Geographical Information Systems. Geographical Information Systems (G.I.S) have been used for some time by government agencies and businesses to help assess the potential damage to humans and the environment. Dr. Padgett reminded those in attendance that although those systems have proved beneficial in the past, many of the systems now in use are entirely out-dated. He continues with this line of thought by discussing several instances where professional G.I.S's were conducted without taking into consideration special circumstances of local communities.

According to Dr. Padgett, researchers are working to develop a system of obtaining cultural geographic information as well as eco-graphic information. One assertion made by Dr. Padgett is that economic circumstances only slightly impact on the probability that a minority person will live in a polluted home area Dr. Padgett continued on to state that over the course of his studies, he has observed that an increase in family income levels did not correlate to a reduction in exposure to environmetal hazards.

Dr. Padgett may benifit EHAP's pursuit toward the equitable distribution of environmental hazards . His talk was quite scientific and provided good information to the audience. The message was clear and concise. If we brought him in as an expert, I would recommend that he focus solely on environmental geography, and leave the environmental equity background material to persons better able to provide such information.

Industry Strategies in a Changing World

Implementing common standards of compliance at domestic and international industrial facilities

Presenter: *Jennifer l. Kraus, MPH, CHMM, Dames & Moore, Inc., San Diego, California*

Ms. Kraus was unable to present her paper in New Orleans. Fortunately, she asked one of her colleagues, Mr. William Goodson, to present the paper in her absence.

Mr. Goodson did an admirable job in presenting Mrs. Kraus's findings. The central theme of the presentation evaluated the need to establish standardized compliance regulations at domestic and international facilities. Supporting data was substantiated by real life case studies. The case studies selected were based on individual companies ability to transcend international regulatory differences. International regulations were evaluated to establish compliance guidelines for use throughout the organization.

The problems involving international compliance rates also cause ethical concerns. For instance, if 100 PPB is a satisfactory rate for chemicals in a developing third world country, while 50 PPB is the required level for compliance in the United States, which level should ultimately be used? Should the company place its new facilities in the third world country, or should the company reduce the emissions in the third world country to 50 PPB's as well.

It may be beneficial in the future to contact Ms. Kraus and acquire copies of her research. At this time I am unsure of the international direction of EHAP, but this area of risk compliance could prove quite useful for a wide variety of domestic firms. The authors conclusion, that industry's commitment to compliance, transcending regulatory requirements, results in quantifiable benefits should serve as a springboard that governmental agencies and businesses could adapt. This adaptation would not just be limited to international regulatory differences, but also differences in interstate commerce laws and regulatory variances.

Industry Strategies in a Changing World

Environmental Ethics

Presenter: *James A Spangler, Barrett Kays and Associates, P.A., Raleigh, NC*

Mr. Spangler asserted in his presentation overview that it was his intent to "examine various environmental permitting strategies employed by those seeking permit approvals, and by those who issue the permits". Unfortunately, the presentation that followed incorporated limited focus on those seeking approvals, and much more on those that are in charge of the actual permitting.

Mr. Spangler's presentation invoked hostility from most of the participants attending the session. As mentioned before, Mr. Spangler's presentation focused on governmental regulators much more frequently than businesses. According to Spangler, regulatory agencies often go beyond environmental compliance based motivations, and instead focus on monetary benefits to the agency. Unfortunately, Spangler bases a great deal of his findings on unidentified sources inside the very agencies that he criticizes. Because of this, those in the audience (including some of the agencies he listed) questioned the intent and motivations of the author as well as the research techniques used.

What Mr. Spangler may have attempted to assert is that businesses and agencies need to incorporate strategic permit planning into their overall strategic planning. Without such planning, many companies may run the risk of being fined and complianced out of existence.

The delivery of this presentation left much to be desired. The author used questionable research technique in securing his information. The information that was gathered was presented in a very biased manner. I felt Spangler should have been better prepared to defend his position on governmental agency motivation. Having recently earned his masters in public policy from Duke University, Mr. Spangler should have anticipated the reaction of the audience and tailored his delivery as such.

How to Prevent and Resolve Public Controversy

Presenter: *Desmond M. Connor, Ph. D. Connor Development Services Ltd.*

Dr. Desmond Connor, an expert in the field of public controversy resolution, moderated he second scheduled NAEP pre-conference seminar held on Sunday, June 12. Dr. Connor condensed his normally one to two day workshop into a concise, three hour abbreviated version.

The central theme of the workshop focused on realizing the real information and social needs of a community, providing correct information to the public, community involvement in environmental assessment and reducing public frustration and controversy concerning environmental risks. The session sought to broaden the environmental professionals concepts of constructive citizen participation and gain insights into changing social climates. Other topics addressed included activating the usually silent majority of a community and addressing the reasons why people resist change.

Des Connor is a consulting sociologist and President of Connor Development Services Ltd. of Victoria, B.C. Over the course of the last two decades he has designed and managed over 220 public consultation and social impact assessment programs across Canada and the United States. During his session, Dr. Connor utilized group involvement and interaction to incorporate real life situations and risk communication theory. As the session progressed, participants jotted down responses to questions proposed by Connor. Those responses were then shared with others in the group and were combined to form a consolidated listing of problems and solutions. Participants were then asked to rank the items in order of importance, allowing those topics felt most important to be given priority.

Dr. Connor extensively utilized video tapes to supplement group discussion of various topics. He seemed to focus a great deal of energy in presenting the correct way of sponsoring a public open house. According to Dr. Connor "The traditional public meeting, which often seems like the last of the blood sports, frequently generates a high level of anxiety, reinforces opposition groups and generates more heat than light on the object. As a result of many such experiences, the Open House, modeled on its real estate analog, was developed in the early 1970's. The Open House visitor is free to determine at what time they visit, how long they stay, and what questions they ask." . Although an Open House may not be practical for EHAP purposes, the idea may be worth looking into more closely.

I suggest that we keep Dr. Connor in mind as a possible expert for future Crossroads events. He presented well and seemed extremely focused,. Of the twenty five or so persons that attended the session, I spoke with perhaps eight. Of those eight, each seemed to gain some insight into new strategies for developing community involvement.

National Association of Environmental Professionals

June 11 - 15, 1994
New Orleans, Louisiana

Report by Sylvia Rivers

The National Association of Environmental Professionals
"Global Strategies for Environmental Issues"

SESSION 1:

How to Prevent & Resolve Public Controversy

Desmond Conner, PhD
Conner Development Services Ltd.

This speaker has his own consulting firm in Canada, designing and managing public involvement programs for corporations and government agencies who are seeking public acceptance of new policies & projects.

He shared many techniques for balancing vocal communication and confrontation when the majority/minority opposes a new policy or program. (see handout)

Basically, Conner believes you must know your community and have an understanding of their resistance to change. There exists in any one community many **publics**-not just one public-and you must know who your opposition is and who your supporters are.

Identify and involve your supporters. Devote no more than 20% of your time and money to your opposition. (It is virtually impossible to change the minds of your opposition, so spend time on your supporters.)

You must develop community understanding of your project by educating them on your project and supplying them with an opportunity to receive two-way information (communication not confrontation)

This can be implemented with telephone surveys, personal contact, and media communication.

A citizen participation plan should be carried out **during the technical planning of your project.** You will gain considerably more support from your public if they are part of the planning process.

An open house and/or planning workshop opens ways for constructive involvement by different publics. Give them alternatives and suggestions to discuss and your relationship will be a lot more productive.

SESSION II: THE NATIONAL ENVIRONMENTAL GOALS PROJECT

This session briefed members of NAEP on where the EPA's National Environmental Goals Project presently stands.

The National Environmental Goals Project is being set up by the EPA and will outline specific measureable goals to evaluate the nation's progress in environmental protection. (the EPA's job being to protect the public health and the environment).

An outline of the project is attached. It is still in the drafting stages and the EPA will seek public involvement and cooperation from sister federal agancies, (particularly the departments of Interior, Energy, Agriculture and Commerce), to help develop the policy and and finalize the goal-setting. The final draft of the project goals will be announced on Earth Day in April 1995 and will be achievable by the early years of the 21st century.

The EPA's mission is "to protect citizens public health and the environment" and they have found the public perception of risk to be different that the scientific perception of risk. They want to base this project on a three-tiered structure of goals (see pamphlet) based on science, public/political realtieis and policy positions under risk management. The policy will be based on "good quality science". and will proceed in three stages. The first phase (Oct. '93-Jan. '94) is to identify problem areas for which the goals will be prepared. The second phase (Jan.-June '94) is to hold public meetings, co-hosted by the federal and the individual state governments. In the third phase (June '94 - April '95), goals will be finalized, reviewed by the public and then released. This approach is under disuccion and the EPA encourages the views of the states at any point while the process is underway.

To stay involved with this project could benefit EHAP in establishing its goals; to help establish a public/professional outreach program; help in developing our database of talented scientists and experts in cleanup activities; help us make contacts in the public, and educational world ; help us in establishing a holistic approach to recurring health and risk issues, etc....

I think it would be beneficial for EHAP to observe the processes they are taking to develop their goals because their process is similar to ours. Perhaps one person could track their results, attending public meetings and researching the process of obtaining their goals.

As stated in our grant proposal, EHAP is to bring together the resources of other colleges, universities, professional societies, and federal agencies, i.e. the EPA in pursuit of excellence. To stay involved with their project could benefit us greatly.

Have the Facilitator lay the ground rules
-Instruct the audience to be courteous, be hard on the issues, soft on each other.
-It's OK to disagree but listen to others as an ally
-Everyone should participate and no one should dominate
-Honor the time limits

Group Members Role
Contribute ideas
Listen to others ideas
state concerns openly

Recorder's Role
-Court reporters are not needed.
-Have someone in the front of the room creating a visible record of the meeting.
-Have them write down the group's ideas in their words, using key words
-This provides a visual record to help the group stay focused

Facilitator's Role-Post Meeting
-Restates the "Group memory"
-Brings up the unanswered questions & attempts to get them answered for all parties
-Assures that all followup steps anre completed in a timely manner (the group memory must be mailed out to the participants in a timely manner)

ADVANTAGES OF HAVING A FACILITATOR
-Frees parties to concentrate on content of meeting
-Fairness
-Manages confrontation
-Efficiency
-Records information in short form
-Immediate feedback
-Thoroughness
-Removes Targets
-helps alleviate suspicion & is able to manage the meeting free of attacks

DISADVANTAGES
-Need time to prepare objectives thoroughly
-Loss of control
-Cost - you have to pay the facilitator
-Biased facilitation - must find a non-biased facilitator

Common Pitfalls in Public Meetings
-Objective-not clearly defining your objectives
-Timing errors
-Community leaders-
-Physical setting
-Becoming a target

Traits on Public Meetings
-People avoid making decisions
-People like to have a say-and that it has been listened to
-Most people don't like to be told what to do
-Results aren't made by dwelling on the negative
-Doubt-no settlement is ever made without a degree of doubt

When planning a meeting, you must establish your **purpose** with all parties hosting the meeting. The scoping process will help you identify issues, inform the publics and identify the stakeholders.

Key Elements of /Setting Up Your Public Meeting
-Meeting Purpose Established: Premeeting Assessment, Context, Stakeholders, Desired Outcomes and Topics Covered, Specific Objectives and outputs established
-Attendees, Roles and Room Arrangements
-Decision-Making Method
-Detailed Agenda Planning

Set up the room auditorium style, with two newsprint pads on easles.
Don't sharte your mic with anyone else because they will grab it-soapbox style

Other things discussed...

When dealing with difficult people, accept that they are difficult, listen to them and acknowledge theat you have heard them...then deal with them. Confront them if you must, but move on - Defer them to Group Memory...Agree/Disagreee then move forward.

Stakeholders are affected by the decision that is being made...they can block your decision and need to be involved during the implementation period.

During the meeting, hand out the drafted EIS and have the agenda on a handout. Lay out the decision process and then explain the appeal process so that everyone understands.

Have the meeting in a location that is easily accessable by public transportation (if that is an important issue in your city).

Don't send out press releases or agendas without the starting time and ending time.

Produce a mail-back form....Send out a summary of all that was discussed. Make it a three-fold with a tear-off sheet for mailing back with additions/comments.

LOWERING RISK PANIC BY EFFECTIVE COMMUNICATION

The Policy of Risk VS. Invdividual Risk:
Key to Effective Risk Communication
Ronald Gots, MD, Ph.D, National Medical Advisory, Bethesda, Maryland

This was an excellent session on the communication of environmental health risks. Ironically, the guiding principles of environmental regulation can be different than what is actually determined by a scientist to be a health risk.

The EPA has never been designed to communicate with individuals about personal risk...the technical explanations do not reassure a citizen who has fears of health risks when being exposed to a hazard.

Dr. Gots is a toxicologist who has expertise in risk assessment. His theory is this:

People want answers. They want to know if the hazard will hurt them and how we know if it will or won't.

Regulatory policies set up public health measures that don't necessarily coincide with personal risk...they are usually set at a lower standard than the likelihood o f developing personal risk. Communicators and physicians must understand this. For instance, environmental companies
come in and give the public numbers (there are 12 parts/billion of xyz in the water...5 parts is the regulatory guideline=instant public panic). This is not effective communication because this could transform into risk panic. Regulatory knowledge should be explained away when risk communicating. For instance, the public views the EPA standards as sacred--below the number is safety and above it is danger The public will need reassurance and the EPA is not designed to deal with this. Moreover, rules involving maximum contaminant levels in air or water have little direct application to the individual.

The public has a right to know between known and theoretical hazards. Without such an understanding, the citizen will never know what 15 ppb in his Perrier means or how deeply the community should dig into their pockets for evironmental clean-up.

Doctors are frequently uninformed on chemical effects, emmission effects. As technology development grows, the risk communication profession grows.

Early on, communicators should be honest and effective communicators. Technical knowledge is essential and people skills are necessary.

Read...Technological Risks by WH Lewis and read the Sandman

5 of 5

RAY GERMANN - works for the public and community relations office

The speaker, Ray Germann gave an interesting talk on a project in Hungary that he was involved in during the midst of the privatization of Hungary's government-owned properties. The Hungarian Electricity Board began upgrading several power plants during 1992 and conducted environmental feasibility studies at three plants as well as an environmental risk communication program. The risk communication program was designed to inform the public on the true health and environmental risks posed by the project and to gather public input into the process. The ultimate goal, of course, being to proceed with the project without opposition or public intervention.

Environmental Resources Management company was hired to perform the environmental assessements and to conduct risk communication programs in three cities. The presentation that Germann gave focused on the methods used to perform risk communication in a country still adapting to democracy. It reflects the challenges faced by the project team in identfying and dealing with new political leaders and non-govt. organizations.

The result was an intricate network of community and government representatives at the local, regional and national levels. This network functioned as an information-sharing vehicle which allowed all affected parties to better understand the health risks of the project. It also helped to balance the risks with the benefits of the project.

How it was done:

Found out who the audience was and the best way to communicate with them. Wanted to incorporate the public opinion in to the study process.

Challenges: Identifying the appropriate public audiences
Educating the audiences on how to best participate in the process
Dealing with the diverse & conflicting organizations and communities
Decipher true agendas and motivation early on

Three Step Process:
-Assessment - Information gathering
-Planning - Information processing and strategy development
-Implementation - Outreach activities

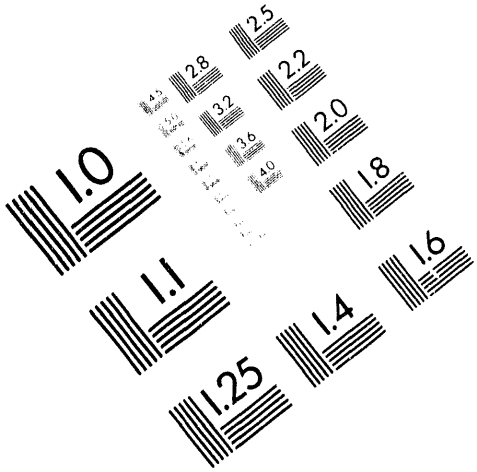
Assessment Findings
-Public groups diverse, disorganized and fragmented
-Local and state government in a state of flux
-NGO's powerful opinion leaders
-Participation by individual citizens limited

Planning Basics
-Need to reach all audiences simultaneously
The public didn't trust elected officials and govt regulators

-Communications held in an open forum
-Substantial education on how to participate
-Special emphasis on demonstrating public effectiveness

Implemented three public meetings
-NGO's, citizens, elected officials, 1/2 hour presentation, 1/2 hour question and answer period
-Besides public meetings, had fact sheets-information from technical people
-Meetings with environmental authority
-Strong follow-up - continuous two-way dialogue
-Briefings - small group

Gave clear info of true risks
Full disclosure of uncertainties
Responsive to concerns
Acting on concerns



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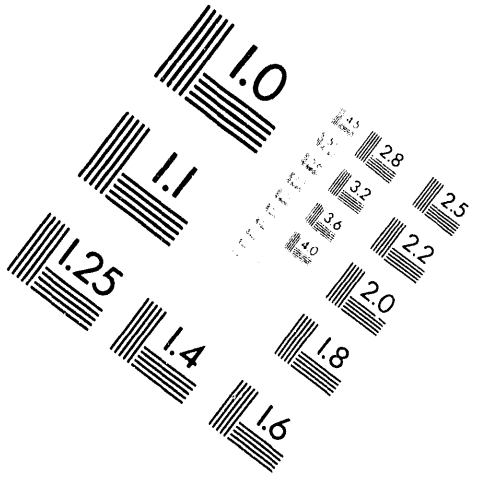

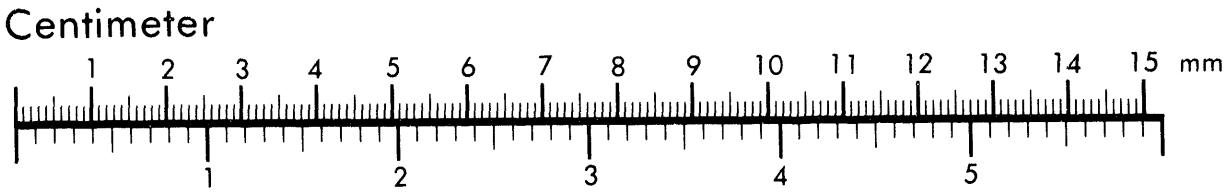

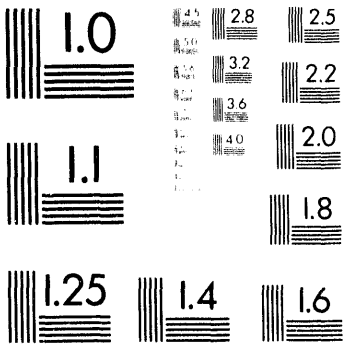

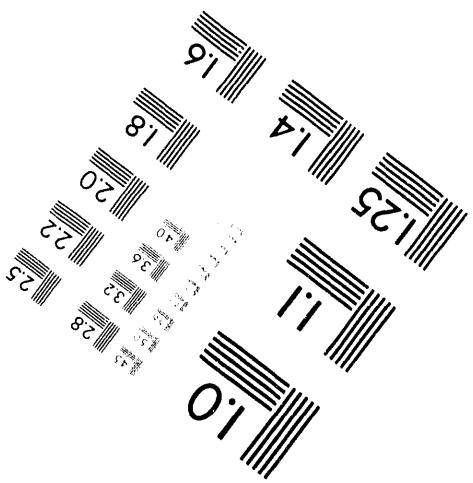

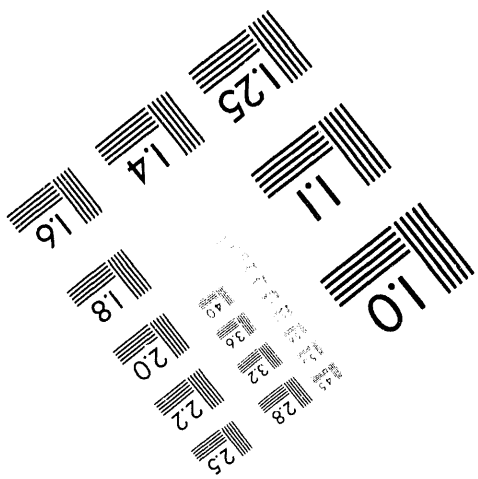

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