CHEMICAL MANUFACTURERS ASSOCIATION

April 15, 1994

Dear Vinyl Chloride Research Coordinators:

The next VCRC meeting is scheduled for May 19, 1994. The agenda for the meeting is enclosed. Also enclosed are: 1) a draft scope of work for an update of the mortality among vinyl chloride workers; 2) an historical perspective on inter-industry vinyl chloride study; and, 3) the benefits of updating the inter-industry study of vinyl chloride workers. Please review these documents in conjunction with Dr. Richard Reitz's abstract on physiologically-based pharmacokinetics model for vinyl chloride and the ATSDR Federal Register notice on vinyl chloride research data needs that were sent to you with my March 30 letter.

I am looking forward to seeing you on May 19.

Sincerely,

Has Shah

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel

Enclosures

SL 107216

2501 M Street, NW, Washington, DC 20037 Telephone 202-887-1100 Fax 202-887-1237

CHEMICAL MANUFACTURERS ASSOCIATION

Vinyl Chloride Panel

Vinyl Chloride Research Coordinators

Tentative Agenda

DATE: May 19, 1994

TIME: 10:00 a.m. - 3:00 p.m., EDT

PLACE: CMA Offices
2501 M Street, NW
Washington, D.C.

1.0 Approval of February 14, 1994 Record of Meeting

2.0 Discussion of Scope of Work of the Epidemiology Study

3.0 Discussion of Potential Contractors for the Epidemiology Study

4.0 Discussion of Cost Sharing Formula for the Epidemiology Study

5.0 Presentation by Richard Reitz on Predicting Cancer Risk from Vinyl Chloride Exposure with a Physiologically-Based Pharmacokinetic Model - TENTATIVE

6.0 Discussion of Course of Action with EPA on Vinyl Chloride Risk Assessment

7.0 Discussion of ATSDR Research Data Needs for Vinyl Chloride

8.0 Discussion of Course of Action with ATSDR on Its Priority Data Needs

9.0 Financial Statement

10.0 Schedule Date for Next Meeting or Conference Call

Scope of Work
Company Commitments
Invited Experts
Cancer Risk Exposure Issue
Cancer Risk response

Has Shah

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel

Subject to Approval

SL 107217

ANTITRUST CHECKLIST FOR CMA MEETINGS

This antitrust checklist is for use by CMA staff and member representatives in the conduct of CMA-sponsored meetings. *Prohibited discussion topics apply equally to social gatherings incidental to CMA-sponsored meetings.* The Checklist is not exhaustive and does not address antitrust issues relating to activities other than CMA meetings. Participants in CMA meetings also should be thoroughly familiar with: (1) "Antitrust Guide for CMA Committee Members;" and, (2) "General Principles Applicable to the Structure and Operations of Committees." Both of these documents may be found in the CMA Directory.

DO

Ensure strict performance in areas of:

OVERSIGHT/SUPERVISION:

- Have a CMA staff representative at each CMA-sponsored meeting (unless an exception has been authorized by the appropriate CMA vice-president);
- consult with an attorney of the CMA Office of General Counsel on all antitrust questions relating to CMA-sponsored meetings;
- limit meeting discussions to agenda topics (unless additional topics have been approved by the appropriate CMA staff representative); and
- provide each member company representative and CMA staff representative attending a CMA-sponsored meeting with a copy of this checklist, and have a copy available for reference at all CMA-sponsored meetings.

RECORDKEEPING:

- Have an agenda and minutes which accurately reflect the matters which occur;
- provide agendas and minutes to the CMA Office of General Counsel for review and approval in advance of distribution; and,
- fully describe the purposes and authorities of all task groups, work groups, ad hoc or other standing committee subgroups in the minutes of the appropriate parent committee.

VIGILANCE:

- Protest against any discussion or meeting activities which appear to violate this checklist; disassociate yourself from any such discussion or activities and leave any meeting in which they continue.

DON'T

Do not, in fact or appearance, discuss or exchange information on:

PRICES, INCLUDING:

- Individual company prices, price changes, price differentials, markups, discounts, allowances, credit terms, etc.;
- individual company data on costs, production, capacity, inventories, sales, etc.; and,
- industry pricing policies, price levels, price changes, differentials, etc.

PRODUCTION, INCLUDING:

- Plans of individual companies concerning the design, production, distribution or marketing of particular products, including proposed territories or customers; and,
- changes in industry production, capacity or inventories.

TRANSPORTATION RATES:

- Rates or rate policies for individual shipments, including basing point systems, zone prices, freight equalization, etc.

MARKET PROCEDURES, INCLUDING:

- Company bids on contracts for particular products; company procedures for responding to bid invitations; and,
- matters relating to actual or potential individual suppliers or customers that might have the effect of excluding them from any market or influencing the business conduct of firms toward them.

CONSENT DECREE SUBSTANCE:

- Any matter relating to trisodium phosphate (a restriction required by a 1962 consent decree to which CMA is a party)

Revised 3/80 (single page version)
Reformated 1/89 MDB

SL 107218

APPLIED EPIDEMIOLOGY INC.

SL 107219

April 4, 1994

Hasmukh C. Shah, Ph.D.
Vinyl Chloride Panel
Chemical Manufacturers Association
2501 M Street, NW
Washington, D.C. 20037

Dear Dr. Shah:

As you suggested in our brief telephone conversation about two weeks ago, I am writing to express my interest in preparing and submitting a proposal should the Chemical Manufacturers Association decide to update the vinyl chloride cohort study. This study has provided valuable information on a large sample of employees occupationally exposed to vinyl chloride, and should continue to elucidate a number of important issues.

My colleague Dr. Harris Pastides and I have worked with CMA on a number of occasions, mainly with Ms. Sandra Tirey and the Epidemiology Task Group. We authored the CMA Occupational Epidemiology Resource Manual, a practical guidebook on establishing epidemiology programs and conducting epidemiological research. Related to this, we presented an Epidemiology Resource and Information Center (ERIC) Workshop on "Establishing and Maintaining an Effective Occupational Epidemiology Program." Most recently, we authored another CMA manual entitled, Establishing an Occupational Epidemiologic Surveillance Program: A Resource Guide.

We have worked and continue to work with several member companies, and have established excellent relationships with many of their corporate epidemiologists. Perhaps the most recent and relevant of this work is a

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cohort mortality study of employees in the VCM and PVC division of the Vista Chemical Company, which will begin this month.

I have enclosed a copy of my *Curriculum Vitae*, and will be happy to send additional information, including Dr. Pastides's *CV*, if needed.

We look forward to discussing with you the prospects of assisting with this research. Please do not hesitate to call me if you have any questions or need additional information.

Sincerely yours,

Kenneth A. Mundt, Ph.D.

enclosure

SL 107220

Curriculum Vitae

KENNETH ARTHUR MUNDT, Ph.D.

CURRENT POSITIONS

Assistant Professor (1989-present)

Department of Biostatistics and Epidemiology
School of Public Health
403 Arnold House –
University of Massachusetts
Amherst, MA 01003

Telephone (413) 545-2861
Fax (413) 545-1645

Visiting Associate Professor (1991-1996)

Institut für Epidemiologie und Sozialmedizin
Universität Münster
Von-Esmarch Straße 56
D-48129 Münster GERMANY

Telephone 49 (251) 83-5520
Fax 49 (251) 83-5300

Senior Epidemiologist (1991-present)

Applied Epidemiology, Inc.
P.O. Box 2424
Amherst, MA 01004

Telephone (413) 256-3556
Fax (413) 256-3503

EDUCATION

Ph.D., Epidemiology

University of North Carolina at Chapel Hill,
Chapel Hill, North Carolina, 1990.

M.S., Epidemiology

University of Massachusetts at Amherst,
Amherst, Massachusetts, 1986.

M.A., English

University of Virginia at Charlottesville,
Charlottesville, Virginia, 1982.

A.B., English

Dartmouth College,
Hanover, New Hampshire, 1981.

UNIVERSITY RESEARCH

1994

Principal Investigator
Healy Endowment Award. Lead Prevalence Study
(1993-4) $5,000

Co-Principal Investigator
Occupational Upper Extremity Disorders Clinic
University of Massachusetts Medical Center
(1993-4) $57,000

Principal Investigator.
E.I. Du Pont de Nemours Company. Educational Aid Program. Occupational Epidemiology Unit.
(1992-4) $15,000/year

1993

Principal Investigator/Convenor.
Second National Conference on Occupational Surveillance, University of Massachusetts, Amherst, MA.
(March 9-11, 1993) $26,000

Co-Investigator.
Chemical Manufacturers of America. Definition and Strategies for Developing Occupational Surveillance.
(1992-3) $38,000

Principal Investigator.
Faculty Research Grant. Epidemiological Surveillance.
(1992-3) $4,940

1992

Principal Investigator.
Faculty Research Grant for Conference/Performance Travel.
Third Annual Symposium on Environmental and Occupational Health in Central & Eastern Europe in Poland.
(1992) $600

Co-Investigator.
Occidental Chemical Corporation. Development of a Corporate Epidemiological Surveillance System.
(1991-2) $50,000/year

1991

Principal Investigator/Convenor.
National conference, "Occupational Surveillance"
University of Massachusetts, Amherst, MA.
(April 28-30, 1991) $22,000

1990

Co-Investigator.
Chemical Manufacturers of America. Development of Resource Materials for Occupational Epidemiology.
(1990) $75,000

UNIVERSITY RESEARCH (continued)

1990 (cont'd)	Principal Investigator. National Institute of Occupational Safety and Health. Immuno-Epidemiology of Crab-Induced Occupational Asthma. (1989-1990) $43,500.
1989	Principal Investigator. United Way of North Carolina. Immuno-Epidemiology of Crab-Induced Occupational Asthma: Pilot and Preparatory Phases. (1989) $4,000.
	Principal Investigator. Biomedical Research Support Grant, School of Public Health, University of North Carolina. Production of Antigen Solutions for Skin Testing. (1988-1989) $5,886.

RELEVANT EXPERIENCE

1994	Guest Editor, Journal of Ambulatory Care Management "Epidemiological and Managerial Challenges in the Workplace" Volume 17(2), April, 1994.
1993 - present	Director, Occupational Epidemiology Unit School of Public Health, University of Massachusetts.
1993 - present	Consultant to the Medical Director, The World Bank, Washington, D.C.
1993 - present	ATSDR Peer Reviewer in Epidemiology.
1993	Member, 1993 Internship Program Objective Review Committee, Association of Schools of Public Health/Centers for Disease Control/Agency for Toxic Substances Disease Registry.
1992 - present	Founder and Director, Surveillance Resource Center, Occupational Epidemiology Unit.
1992 - present	Epidemiologist, Northeast Regional Environmental Public Health Center, School of Public Health, University of Massachusetts.
1992 - present	Member, Human Subjects Committee, School of Public Health, University of Massachusetts.
1991-1993	Assistant Director, Occupational Epidemiology Unit, University of Massachusetts

RELEVANT EXPERIENCE (continued)

1991 - present	Member, Union Carbide Scientific Board of Advisors.
1990 - 1992	Member, International Chrome Development Association, Health, Safety and Environment Committee, Paris, France.
1990 - 1992	Epidemiologist, Chromium Environment, Health and Safety Committee, Industrial Health Foundation, Pittsburgh, PA.
1988 - 1989	Research Assistant to Carl M. Shy, M.D., Dr.P.H., on Oak Ridge Universities Occupational Studies of Department of Energy Employees, and on North Carolina Dusty Trades Occupational Health Studies, University of North Carolina.
1988 - 1989	Visiting Researcher, Duke University Marine Biomedical Center, Duke Marine Laboratory, Pivers Island, Beaufort, North Carolina.
1983 - 1984	Commissioned Officer Student Training Extern Program (COSTEP). United States Public Health Service, Health Resources and Services Administration, Silver Spring, Maryland.

TEACHING EXPERIENCE

1989 - present	Assistant Professor University of Massachusetts, School of Public Health: "Principles of Epidemiology" "Applied Epidemiology" "Occupational Epidemiology" "Special Topics in Occupational Epidemiology" "Departmental Doctoral Seminar" Numerous Independent Study Projects
1987 - 1988	Teaching Assistant to David G. Kleinbaum, Ph.D. University of North Carolina, School of Public Health. "Special Topics in Epidemiological Methods" "Advanced Methods in Epidemiology"

SHORT COURSES

1993, 1994	Applied Epidemiology, Inc. and Akademie für offentliche Gesundheit , Wermelsckirchen, Germany: "Intensive Course in Occupational Epidemiology"

SHORT COURSES (continued)

1991 Cancer Registry of Norway, Oslo, Norway. August 12-16:

"Occupational and Environmental Epidemiology"

1989, 1990, 1991 International Summer School for Epidemiology, World Health Organization and the Akademie für offentliche Gesundheit , Bochum, Germany

"Occupational and Environmental Epidemiology"

HONORARY AND PROFESSIONAL SOCIETIES

American Conference of Governmental Industrial Hygienists (Full Member)

American Public Health Association

Delta Omega, Public Health National Honor Society

International Society for Environmental Epidemiology

Sigma Xi, Scientific Research National Honor Society

Society for Epidemiologic Research

PRESENTATIONS

1994

Birk T, Mundt KA, Schumann J, Person M, Weiland S, Keil U. "Cost-center Accounting Codes ("Kostenstellen") as Exposure Indicators in an Epidemiological Study of the German Rubber Industry." Conference on Retrospective Assessment of Occupational Exposures in Epidemiology, Lyon, France, April 13-15, 1994.

Weiland S, Birk T, Mundt KA, Person M, Schumann J, Keil U. "The Epidemiologic Study of Cancer in the Rubber Industry in Germany: An Update." International Conference on Occupational Health in the Rubber Industry, The Netherlands, May 31-June 1, 1994.

1993

Mundt KA. "Occupational Epidemiology in a White-Collar Setting." Invited Speaker, The World Bank, May 11-12, 1993.

Mundt KA. "Occupational Surveillance: Concepts and Goals." Second National Conference on Occupational Surveillance, University of Massachusetts, Amherst, MA, March 9-11, 1993.

PRESENTATIONS (continued)

Mundt KA. "Practical Stretegy for Developing Epidemiological Surveillance." Design and Analysis Workshop, Second National Conference on Occupational Surveillance, University of Massachusetts, Amherst, MA, March 9-11, 1993.

1992

Mundt KA and Weiland S. "The Association of Asthma Symptoms and Allergic Rhinitis with Traffic Density on Street of Residence." Annual meeting of the International Societies for Environmental Epidemiology and of Exposure Analysis, Cuernavaca, Morelos, Mexico, August 26-29, 1992.

Pastides H and Mundt KA. "Retrospective Estimation of Exposure to Hexavalent Chromium in an Occupational Cohort." Annual meeting of the International Societies for Environmental Epidemiology and of Exposure Analysis, Cuernavaca, Morelos, Mexico, August 26-29, 1992.

Pastides H and Mundt KA. "Epidemiological Occupational Surveillance." Surveillance in Europe and the EEC, Devonshire Park Centre, Eastbourne, Sussex, United Kingdom, July 1-3, 1992.

Mundt KA. "Occupational Surveillance as a Strategy for Policy Development and Disease Prevention." Protecting Workers, the Environment and Health in a Market Economy: Translating Science into Policy and Action. The United States-Central and Eastern Europe Exchange for Occupational and Environmental Health, third annual symposium, Pultusk, Poland, June 26 - July 1, 1992.

Pastides H, Austin R, Lemeshow S, Klar J, Noess R, and Mundt KA. "A Retrospective Cohort Study of Health Risks Among Chromate Production Workers." Annual Meeting of the Society for Epidemiologic Research, Minneapolis, MN, June 10-12, 1992.

Weissman L and Mundt KA. "Prevalence of Immediate Hypersensitivity in Black Women: A Re-evaluation of Skin Prick Test Data from the Second National Health and Nutrition Examination Survey (NHANES II) and Comparison with an Occupational Study." Annual Meeting of the Society for Epidemiologic Research, Minneapolis, MN, June 10-12, 1992.

Mundt KA, Leeser J, Adams R. "Establishing a Mercury Biological Exposure Index (BEI)." American Conference of Governmental Industrial Hygienists (ACGIH) BEI and Threshold limit value (TLV) Committees, Orlando, Fla., March 21-22, 1992.

1991

Mundt KA. "Epidemiological Approach to Occupational Health." Annual Scientific Meeting, Industrial Health Foundation, Pittsburgh, PA, November 6-7, 1991.

Mundt KA. "Role of Epidemiology in an Occupational Medical Department." Bayer Chemical, Leverkusen, Germany, June 19, 1991.

PRESENTATIONS (continued)

Mundt KA. "Occupational Epidemiological Studies and the Social Context." Department of Epidemiology, State University of New York at Albany, April 18, 1991.

Mundt KA. "Use of Skin Tests in Epidemiological Research." Clinical Epidemiology Department, University of Pennsylvania, Philadelphia, PA, March 14, 1991.

Pastides H and Mundt KA. "Establishing an Occupational Epidemiology Program." Chemical Manufacturers Association, Washington, D.C., March 12, 1991.

1990

Mundt KA. "Studies to Document the Healthy Worker Effect." Department of Work Environment, University of Lowell, Lowell, MA, December 11, 1990.

Mundt KA and Miller J. "Use of Industrial Hygiene Data in Epidemiology Research." Occidental Chemical Industrial Hygiene Annual Meetings, Houston TX and Atlantic City, NJ, November 12-14, 1990.

Mundt KA and Shy C. "Occupational Allergies and the Healthy Worker Effect." Annual Meeting of the Society for Epidemiologic Research, Snowbird, Utah, June 12-15, 1990.

Mundt KA. "Health Effects of Vinyl Chloride Monomer (VCM)." Occidental Chemical Company, Plastics and Polymers Group, Berwyn, PA, May 11, 1990.

1989 and earlier

Mundt KA. "Skin Testing for Allergies in an Occupational Setting." Clinical Epidemiology Seminar Series, University of Massachusetts Medical Center, Worcester, MA, December 20, 1989.

Mundt KA. "Immuno-Epidemiology of Crab-Induced Occupational Asthma: Methodological Issues." Visiting Researcher Program, Duke University Marine Biomedical Center, Beaufort, North Carolina, January, 12-13, 1989.

Mundt KA and Heiss G. "Measuring Ankle Systolic Blood Pressure: Interaction Between Ankle Geometry and Method of Applying Blood Pressure Cuff." National Heart, Lung and Blood Institute Seminar, Bethesda, Maryland, November 3, 1987.

Mundt KA and Pastides H. "Microcomputer-Based Instruction: Applications in Epidemiology." Annual Meeting of the American Public Health Association, New Orleans, Louisiana, October 18-22, 1987.

Mundt KA. "Distribution of Selected Mineral Concentrations in Urban Children's Hair." Annual Meeting of the American Public Health Association, Las Vegas, Nevada, September 28 - October 2, 1986.

PUBLICATIONS AND REPORTS

1994

Mundt KA, Dell LD. Neuropsychological effects of environmental dioxins and furans? (accepted for publication) Occupational and Environmental Medicine Report 1994.

Pastides H, Austin R, Mundt KA, Ramsey F, Feger N. Transforming industrial hygiene data for use in epidemiology studies: A case study of hexavalent chromium (accepted for publication) Journal of Occupational Medicine and Toxicology 1994.

Mundt KA. Epidemiological surveillance: A management tool for occupaitonal health. Journal of Ambulatory Care Management. 1994;17(2):20-29.

Weiland SK, Mundt KA, Rückmann A and Keil U. Self-reported wheezing and allergic rhinitis in children and traffic density on street of residence. Annals of Epidemiology 1994;4:79-83.

Pastides H, Austin R, Lemeshow S, Klar J, Noess R and Mundt, K. A retrospective cohort study of occupational exposure to hexavalent chromium (accepted for publication) American Journal of Industrial Medicine 1994.

Gehlbach SG and Mundt KA. Evaluating Worksite Health Programs. Journal of Ambulatory Care Management 1994;17(2):88-94.

1993

Pastides H and Mundt KA. Establishing an Epidemiological Occupational Surveillance Program. Chemical Manufacturers of America, Washington, D.C., 1993.

Mundt KA. Occupational surveillance as a strategy for policy development and disease prevention. In: Proceedings of the Third Annual Symposium on Environmental and Occupational Health during Societal Transition in Central and Eastern Europe. Protecting Workers, the Environment and Health in a Market Economy: Translating Science into Policy and Action, June 26 - July 1, 1992. Published by Management Sciences for Health, Boston, Massachusetts, 1993.

1992

Mundt KA. The Workplace as Laboratory. Business Digest, June 1992;34.

Mundt KA, Chambless LE, Burnham CB and Heiss G. Measuring ankle systolic blood pressure: Validation of the Dinamap 1846 SX. Angiology, 1992:43(7);555-566.

Mundt KA. Letter to the Editor: RE: "Exposure to residential electric and magnetic fields and risk of childhood leukemia" and "Case-control study of childhood cancer and exposure to 60-HZ magnetic fields." American Journal of Epidemiology 1992:135(9);1070-1075.

PUBLICATIONS AND REPORTS (continued)

Health, Safety and Environment Committee, International Chromium Development Association. Health, Safety and Environment: Industry Guidelines. Paris, France, April, 1992.

Pastides H, Miller JR, Mundt KA, Klar J, Adams RF, Olendorf T. A characterization of occupational static magnetic field exposures at a diaphragm-cell and a mercury-cell chlor-alkali facility. Applied Occupational and Environmental Hygiene 1992;7:42-48.

1991 and earlier

Mundt KA. Epidemiological Review of the American Conference of Governmental Industrial Hygienists (ACGIH) Recommended Biological Exposure Index (BEI) for Urinary Mercury. The Chlorine Institute, September 30, 1991.

Pastides H and Mundt KA. Resource Manual for Occupational Epidemiology, Chemical Manufacturers of America, Washington, D.C., 1991.

Walker A and Mundt KA. Feasibility of Conducting an Industry-wide Study of Respiratory Cancer Related to Ceramic Fiber Inhalation, Final Report to Thermal Insulators Manufacturers Association (TIMA), Epidemiology Resources, Inc., Boston, MA, November, 1990.

Mundt KA. Immuno-epidemiology of crab-induced occupational asthma, doctoral dissertation, University of North Carolina, 1990.

Pastides H, Mundt KA, McKnight CJ and Tuthill RW. Formulating case definitions and identifying cases for analysis (computer-assisted instructional software). In "Applied Epidemiology," Centers for Disease Control, Atlanta, Georgia, 1986.

Pastides H, Mundt KA, McKnight CJ and Tuthill RW. Descriptive analysis of the disease outbreak (computer-assisted instructional software). In "Applied Epidemiology," Centers for Disease Control, Atlanta, Georgia, 1986.

Pastides H, Mundt KA, McKnight CJ and Tuthill RW. Formulating and testing hypotheses (computer-assisted instructional software). In "Applied Epidemiology," Centers for Disease Control, Atlanta, Georgia, 1986.

Mundt KA. Distribution of selected mineral concentrations in urban children's hair. Masters thesis, University of Massachusetts, 1986.

Tuthill RW and Mundt KA. An evaluation of hazard abatement activities in selected state-funded lead screening programs, Final report to Massachusetts House of Representatives Post Audit and Oversight Committee, June 27, 1985.

Mundt KA and Polk BF. Identification of site urinary-tract infections by antibody-coated bacteria assay. Lancet 1979;2:1172-5.

Mundt KA and Polk BF. Predictive value of a single diagnostic test: a belated correction. New England Journal of Medicine 1979;300(15):859.

Revised 3/94

POTENTIAL CONTRACTORS

Howard Rockette, Ph.D.
Department of Biostatistics
Graduate School of Public Health
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Pittsburgh, PA 15261

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School of Public Health
Occupational Epidemiology
University of Massachusetts
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(413) 545-6167

Kenneth A. Mundt, PhD
School of Public Health
Dept of Biostatistics and Epidemiology
University of Massachusetts
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Dr. Roy E. Shore
Professor
Environmental Medicine
New York University Medical Center
341 E. 25th Street, Room 204
New York, NY 10010-6500

(212) 340-6500

SL 107230

DRAFT

Scope of Work

Update of Mortality Among Vinyl Chloride Workers

The Chemical Manufacturers Association (CMA) is interested in receiving proposals to update the mortality experience among an established cohort of workers employed in the vinyl chloride/polyvinyl chloride (VC/PVC) industry. This cohort was previously studied by Tabershaw and Gaffey (1974), Cooper (1981) and Wong, et al. (1991).

The Scope of Work for this project is outlined below and includes some key elements which should be addressed in any proposals submitted.

As you will note, the CMA is interested in receiving two major work products at the conclusion of the project: 1) A written technical report summarizing an epidemiologic evaluation of the mortality experience of the workers through 1992 and 2) A manuscript which is suitable for publication in the peer-reviewed scientific literature.

Background

The original records which formed the basis for prior reports of the mortality experience of this cohort are currently in the possession of ENSR Health Sciences located in Alameda, California. If a different study group is awarded the contract to conduct the update study, CMA will arrange the transfer of all pertinent records from ENSR to that contractor. However, ENSR did make confidentiality agreements with some states (see attached list) precluding a direct transfer of death certificates for some of the cohort members. Therefore, submitted proposals will need to indicate how other contractors would proceed to obtain such death certificates for persons dying prior to 1983, the end date for follow-up in the most recent update.

Projected Scope of Work

All proposals submitted in response to this request should address the following issues:

1. Verification of the completeness of the database in comparison with the results of the most recent update (see Wong, et al. 1991, attached.)

2. How to obtain death certificates for employees dying before 1983 which could not be transferred directly from ENSR.

3. Ascertainment of vital status of cohort members who survived through the end of the previous update period (i.e., 12/31/92.)

4. Obtaining death certificates for employees determined to have died after 1982 and assigning a nosologically valid cause of death to each.

5. Conduct of a Standardized Mortality Ratio analysis comparing the cause-specific mortality experience of the cohort with age-, race-, gender-, and period-specific rates for the U.S. male population and individual state male populations. The analyses conducted should consider at least the following factors:

    - Age at first exposure
    - Year of first exposure
    - Type of plant (VCM or PVC)
    - Length of exposure
    - Elapsed time since first exposure

In addition to these points, any proposal should also include the investigators' thoughts on the feasibility and technical merit of the following:

1. Updating the exposure histories of surviving cohort members from 1982 through 1992.

2. Performing internally standardized mortality comparisons using such methods as ~~Poisson~~ regression for comparing SMR's.

POISSON

3

Technical Criteria

You may be interested in some of the criteria that the CMA Vinyl Chloride Research Coordinator's Group will use to evaluate the proposals received. These are listed below for your consideration when preparing your response. The criteria are not listed in any particular order and should not be viewed as having equal weight.

1. The curriculum vitae for each of the scientists who will comprise your project team.

2. Your proposed approach to each of the technical items listed in the Scope of Work.

3. Your proposed schedule for completion of the required deliverable work products listed below.

4. Your description of the technical and physical resources at your disposal for completion of this project.

Required Deliverable Work Products

The deliverables expected by CMA include the following:

1. A series of timely progress reports addressing the following:

    - Verification of completeness of the existing database against the tables presented in the 1986 report to CMA prepared by Wong, et al. (see attachment.)

    - Outcome of efforts to ascertain vital status of cohort members through 1992.

    - Outcome of efforts to obtain death certificates for employees dying after 1982, and for employees dying before 1983 if necessary.

2. A detailed technical report summarizing the epidemiologic analysis submitted to CMA for review and commentary by participating member companies.

3. A manuscript suitable for publication in the peer-reviewed scientific literature, submitted to CMA for review and commentary by participating member companies.

Timing

Investigators wishing to submit proposals should do so by June 15, 1994. CMA would like to receive proposals in two separate documents--one containing the technical proposal and one containing the cost and time-schedule proposals. This will allow us to evaluate the technical merits of the proposal independent of cost and time-schedule considerations. Please supply an original plus ten copies of the technical proposal, and an original plus two copies of the cost/time-schedule proposal.

CMA proposes to evaluate all proposals received in late June 1994, and will select a contractor in July 1994. CMA proposes to award a fixed-price contract to the successful applicant. If your project team prefers a different form of contract, please indicate your preference in your cost proposal.

Additional Information

Please contact Dr. Has Shah at (202) 887-1192 if you have any questions about this request or about contract administrative details. Our lead scientist for this effort is Dr. Jonathan Ramlow of The Dow Chemical Company. You may contact him at (517) 636-1276 with questions about the scientific aspects of this Scope of Work.

Status of ENSR Confidentiality Agreements with Individual States

ENSR had to enter into agreements with different entities to obtain death certificates. In some states, there were no restrictions with whom who we could share, while with others there are variable restrictions. The following summarizes the options by the states that know:

Group A:

States will allow ENSR to give the death certificates to individual companies or CMA as long as we document what is being transmitted

This group includes the following states: Alaska, California, Connecticut, Washington, D.C., Illinois, Iowa, Maryland, Massachusetts, Minnesota, Nevada, Ohio, and Washington.

Group B:

ENSR can provide state file numbers, dates of death, and names to companies or CMA.

This group includes the following states: Colorado, Georgia, Idaho, Indiana, Kentucky, Louisiana, Maine, New Mexico, New York, Oregon, Rhode Island, South Carolina, West Virginia, Wisconsin, and Wyoming.

Group C:

These states require both ENSR and the companies or CMA to write and request the death certificates based on the studies. This involves completing application forms for each state (not all the same), entering the state file numbers, and communicating with each company or CMA. There is then the additional cost of the death certificates.

This group includes the following locations: Alaska, Arizona, Arkansas, Delaware, Florida, Kansas, Michigan, Missouri, Mississippi, Montana, New Hampshire, New Jersey, New York City, North Carolina, North Dakota, Oklahoma, Pennsylvania, South Dakota, Tennessee, Texas, Utah, Virginia, and Puerto Rico.

We are still investigating the process for three states: Hawaii, Nebraska, and Vermont. They have not responded to multiple inquiries.

HISTORICAL PERSPECTIVE ON INTER-INDUSTRY VINYL CHLORIDE STUDY

1960-1963	Report published documenting anesthetic effects in animals and humans and liver injury in animals from chronic exposure.
1967	Acroosteolysis reported in humans exposed to high levels of VCM.
1971	Carcinogenicity of VCM discovered in animals, including angiosarcoma of the liver.
1973	CMA sponsors Tabershaw-Cooper Associates to conduct an epidemiologic study of 8,384 vinyl chloride workers from 34 plants.
1974	First reports of angiosarcoma of the liver cases in VCM workers.
1974	Tabershaw-Cooper report preliminary results confirming high risk of angiosarcoma of the liver and suggesting excess cancers of respiratory system, brain and lymphoma.

GGB 3/15/94

HISTORICAL PERSPECTIVE ON INTER-INDUSTRY VINYL CHLORIDE STUDY

(cont.)

1974	OSHA holds hearings and revises PEL down to 1 ppm.
1981	Cooper expands original epidemiology study to include 10,173 workers from 37 plants--reports show angiosarcoma and brain cancer to be in excess through 1972.
1986	EHA updates inter-industry study with follow-up through 1982--reports angiosarcoma, brain cancer and emphysema to be in excess--no excess respiratory cancer or lymphoma/leukemia.
1991	EHA study is published.
1993	CMA letter to the editor and EHA response are published clarifying the brain cancer and emphysema findings.
1994	CMA Vinyl Chloride Research Coordinators meet to discuss updating study.

GGB 3/15/94

"The study carried out by Environmental Health Associates on behalf of the U.S. Chemical Manufacturers Association is the largest and most informative investigation thus far undertaken."

Sir Richard Doll
Scand J Work Enviorn Health 1988;
14:61-78

GGB 3/15/94

BENEFITS OF UPDATING INTER-INDUSTRY STUDY OF VINYL CHLORIDE WORKERS

- Product Stewardship
  - Demonstrates to workers, community residents, customers, and other audiences our collective commitment to characterize cancer risks associated with employment in VCM/PVC processes.

- Scientific Knowledge
  - Refines the estimate of the number of cases of human angiosarcoma of the liver (ASL) associated with operating VCM/PVC plants in the pre-1972 era in North America.
  - Provides basis for refining human cancer risk assessments which are used by government agencies for permitting facilities, etc.
  - Contributes ASL cases to the international registry.
  - Helps to resolve unanswered questions about alleged links to cancers of the brain, lung, and hematopoeitic system as well as address non-cancer causes of death such as emphysema.

- Litigation Defense
  - VCM/PVC manufacturers continue to face toxic tort litigation alleging that numerous other types (non-ASL) of cancer are related to VCM/PVC employment. This type of research is useful in defending such litigation.

GGB 3/15/94

BENEFITS OF UPDATING INTER-INDUSTRY STUDY OF VINYL CHLORIDE WORKERS

(cont.)

- Chlorine Issue
  - VCM/PVC continue to be a part of the general debate on health and environmental impacts of chlorinated organics. This type of research serves a valuable role in helping to debate the issues on the basis of good science.

GGB 3/15/94

SCIENCE

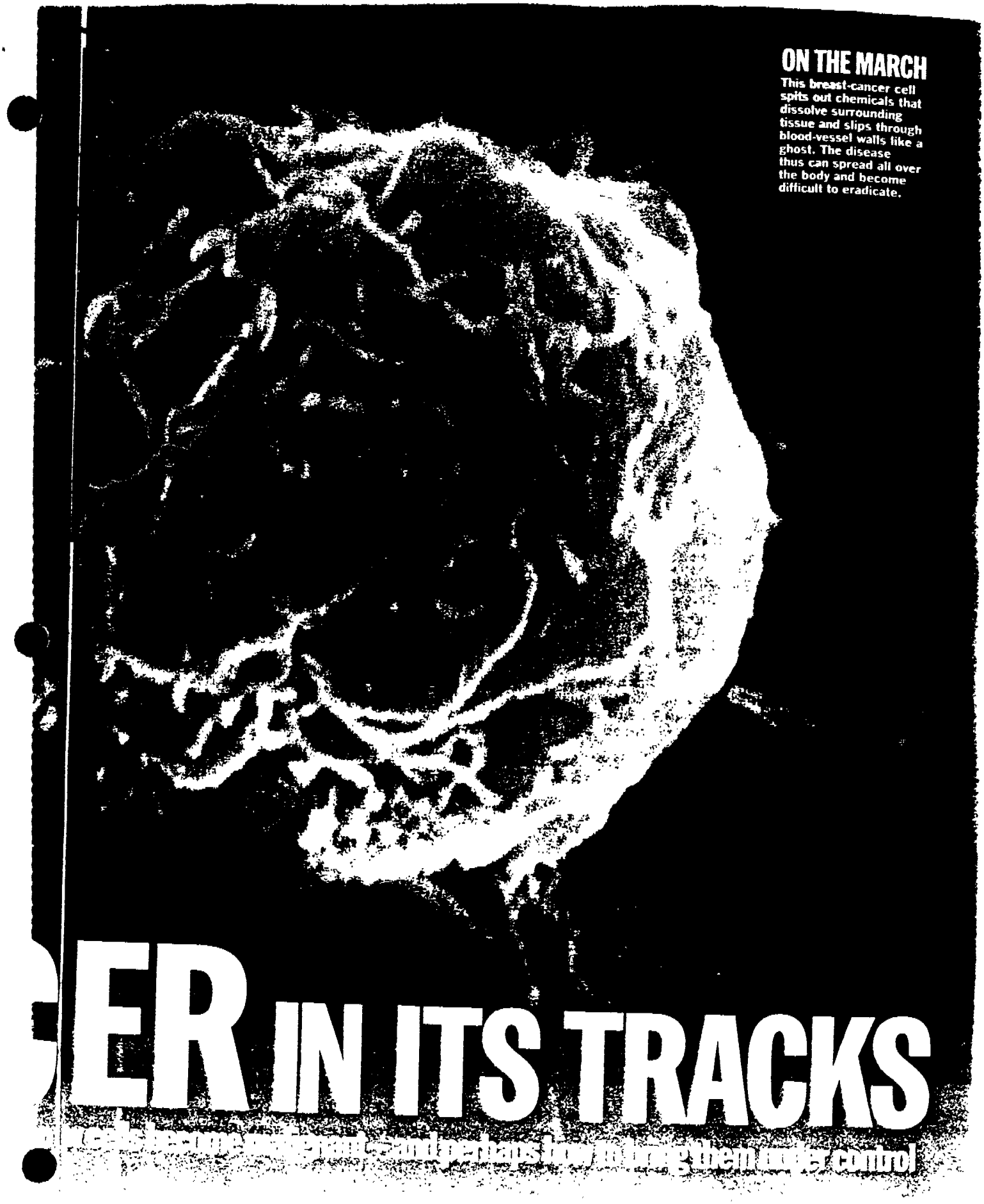
STOPPING CANC

BY J. MADELEINE NASH/CHICAGO

STEALTHY AS A PIRATE SLIPPING FROM A COVE, the cancer cell severs the moorings that attach it to surrounding tissue. Slowly it extends one, two, three fingerlike probes and begins to creep. Then it detects the pulsating presence of a nearby capillary and darts between the cells that compose the blood-vessel wall. It dives into the red river that courses through lung and liver, breast and brain. An hour or so later, it surfaces on some tranquil shore, settles down and—at the expense of its hapless neighbors—begins to prosper.

Gradually the cancer cell invades the turf occupied by its normal counterparts, killing all those in its path. It tricks nearby cells into forming food-bearing blood vessels, then compels them to churn out growth-spurring chemicals. To shield itself from patrolling immune cells, the cancer cell sprouts spiny armor like a sea urchin's. To expel the agents physicians send to kill it, the cancer cell deploys along its membrane a battery of tiny pumps. Is there a way to fight such a foe?

Until now, medicine has tried to overwhelm the cancer cell with brute force, slicing it out with surgery, zapping it with radiation or poisoning it with chemotherapy. All too often, however, a few cells manage to survive the onslaught and germinate, sometimes years later, into tumors that are impervious to treatment. The ability of the cancer cell to outmaneuver its attackers has long been reflected in mortality statistics. Despite gains made against cancers such as childhood leukemia and Hodgkin's lymphoma, the overall death rate remains dismally high. This year more than half a million Americans will succumb to cancer, making it the nation's second



ON THE MARCH

This breast-cancer cell spits out chemicals that dissolve surrounding tissue and slips through blood-vessel walls like a ghost. The disease thus can spread all over the body and become difficult to eradicate.

ER IN ITS TRACKS

GEORGE FREY FOR TIME BACKGROUND NANCY KEDERSHA—IMMUNOGEN/SPL/CUSTOM MEDICAL STOCK

MALFUNCTION The multiple tumor-suppressor gene that Alexander Kamb and his colleagues discovered may explain why these melanoma cells went astray.

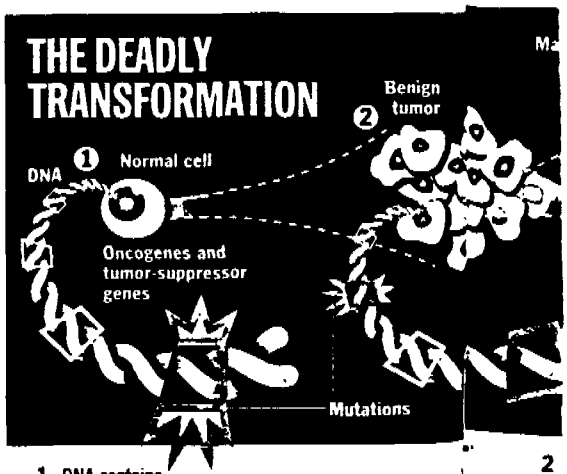
leading killer after cardiovascular disease.

Yet despite the continuing casualties, there is reason to believe the war against cancer has reached a turning point. During the past two decades, a series of stunning discoveries has pried open the black box that governs the behavior of the cancer cell and revealed its innermost secrets. Now the insights gleaned from basic research are being translated into novel approaches to cancer therapy. It still looks difficult to eradicate malignant cells, but scientists are exploring ways to tame them, to make them behave and thus greatly prolong the lives of people with the disease. The new therapies carry the promise of being not only more effective than the current slash-and-burn strategy but also much gentler to the patients who must endure the treatment. Exclaims Dr. Dennis Slamon, a UCLA cancer specialist: "This is the most exciting time imaginable!"

The excitement was running especially high last week, as encouraging news poured out of several labs all at once. From Thomas Jefferson University in Philadelphia came word that an experimental vaccine had given patients unusually long remissions from advanced melanoma, a deadly form of skin cancer. From Canada's McMaster University came a report identifying a telltale enzyme found in cancer cells—but conspicuously absent from most normal cells. If cancer researchers can find a way to deactivate this enzyme, known as telomerase, they may at last have the magic bullet they have long been seeking. Equally tantalizing was the article published in *Science* by molecular biologist Alexander Kamb and his colleagues at Myriad Genetics, a Salt Lake City, Utah, biotech firm. A majority of cancer cells, they found, lack functioning copies of a gene that serves as a circuit breaker and shuts down the abnormal cell growth that causes malignancy. Already Kamb is dreaming up ways to fix this seemingly simple glitch. "The route to therapy," he says, "seems surprisingly clear."

GOOD GENES GONE BAD The conceptual revolution that is just now sweeping into the clinic began in the 1960s, when researchers started to realize that cancer is a disease of DNA, the master molecule that encodes the genetic script of life. One of DNA's most important jobs is to govern cell division, the process by which a cell makes a copy of itself and splits in two. Ordinarily, cell division is tightly regulated, but a cancer cell divides uncontrollably, pushing into surrounding tissue.

A pivotal discovery came in 1976, when Drs. J. Michael Bishop and Harold Varmus at the University of California, San Francisco, made a startling observation. They saw that a viral gene known to cause cancer in chickens was practically a carbon copy of a normal gene found in animal and human cells. The virus had somehow stolen a perfectly good gene and put it to bad use. This finding helped lead to a general conclusion: cells become cancerous because their normal genetic machinery goes awry. The culprits that initiate the damage can be viruses, radiation, environmental poisons, defective genes inherited from parents—or a combination of all of the above.



1 DNA contains oncogenes and tumor-suppressor genes. In a normal cell, these genes work together to control cell growth.

TIME Diagram by Joe Lertola

GEORGE FREY FOR TIME BACKGROUND NANCY KEDERSHA—IMMUNOGEN/SPL/CUSTOM MEDICAL STOCK

By last week researchers had found perhaps 100 cancer genes, at least three dozen of them important in human tumors. Some, known as oncogenes, turn on cell division, whereas others, called tumor-suppressor genes, are responsible for switching the process off. In their normal form, both kinds of genes work as a team, enabling the body to perform such vital tasks as replacing dead cells or repairing defective ones. But mutations in the chemical makeup of these genes, whether inherited or acquired later in life, can disrupt these finely tuned checks and balances. A cell containing a faulty oncogene is often likened to a car with a stuck accelerator, a cell with a damaged tumor-suppressor gene to a car with no brakes.

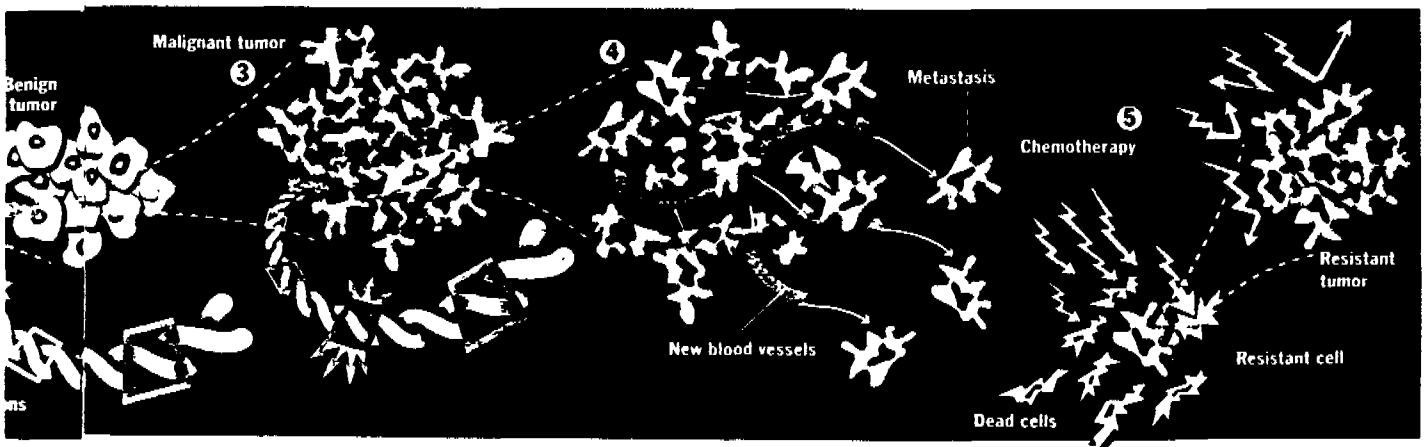
Scientists have thus stripped away cancer's mystery and revealed the malignant cell for what it is: not an intrinsically evil villain but an ordinary machine that has broken down in very specific, and potentially reparable, ways. They have studied the life history of a cancer cell and found errant genes at almost every step of the way, from the initial formation of a tumor to the advanced stages of metastasis, the lethal spread of the disease through the body.

FATAL FLAWS Cancer is not a modern disease. Some of our apelike ancestors undoubtedly suffered from it; so did the dinosaurs. In fact, says Robert Weinberg, a molecular biologist at the Massachusetts Institute of Technology, "it is a risk all multicellular organisms run." Each time a human cell divides, it must replicate its DNA, a biochemical manuscript some 3 billion characters long. In the course of transcribing such a lengthy document, even a skilled typist could be expected to make mistakes, and cells, like typists, occasionally err. More often than not, the mistakes they make are minor and quickly repaired by proteins that serve as miniature mechanics. Occasionally, though, cells with defects in their DNA will continue to divide, eventually forming small growths. The more cell-division cycles an organism undergoes, the more likely it is to accumulate colonies of abnormal cells, each the offspring of a single progenitor. By the time humans reach middle adulthood, then, their bodies contain millions of cells that have taken at least one step toward cancer.

EVEN SO, CANCER IS HARDLY INevitable. For example, 50% of Americans will develop at least one precancerous polyp in their colon at some point, but only a fraction of such polyps will develop into aggressive tumors. Why? Usually it takes so long for colon cancer to unfold that most people end up dying of other causes. Indeed, contrary to popular perception, getting cancer is not at all easy. To begin with, a cell must accumulate mutations not in just one or two genes but in several. In the case of colon cancer, Dr. Bert Vogelstein and his colleagues at Baltimore's Johns Hopkins Oncology Center have shown that a cell must sustain damage to at least three tumor-suppressor genes and one oncogene. The first mutation spurs the growth of the cell, triggering the formation of a benign polyp. Later changes cause the polyp to expand and become increasingly irregular in shape. By the time a cell in this growing mass suffers a final, fateful hit to its DNA, many decades may have gone by.

Clearly, however, some people are at a much higher risk of developing cancer than others, and at an earlier age. For them, heredity plays a major role. Over the past five months, competing teams at Johns Hopkins and Boston's Dana-Farber Cancer Institute have identified four new genes associated with a form of early onset colon cancer known to afflict particular families. These genes are carried by as many as 1 in every 200 Americans, making them the most common cause of cancer susceptibility yet discovered. In their normal form, these biological versions of computerized spelling checkers produce proteins that scoot along strands of replicating DNA, searching for tiny typos. When a protein finds an error in one of the words spelled out by DNA's four-letter chemical alphabet, it flashes an alarm. A person born with only one good copy of any of these genes is fine, until some cell in his or her colon loses or mutates its backup copy. Without a spelling checker, mutation piles upon mutation, telescoping the time it takes for cancer to develop.

BENT OUT OF SHAPE Cancer-causing mutations can occur quite by accident. But chronic exposure to carcinogens—chemicals whose by-products bind to DNA and damage it—greatly accelerate the rate at which dividing cells make errors. Proven carcinogens include asbestos, benzene and some ingredients of cigarette smoke. Many carcinogens, it turns out, are not blunderbusses but leave highly individualized fingerprints in the DNA they touch. At the National Cancer Institute, Dr. Curtis Harris, a molecular epidemiologist, has been examining cells from liver- and lung-cancer patients, searching for mutations in a tumor-suppressor gene known as p53 (p stands for the protein the gene makes and 53 for the protein's molecular weight). Smokers who develop lung cancer, Harris has found, show tiny alterations in the p53 gene that differ from those in nonsmokers. They also vary from the changes found in Chinese



2 Defects in these genes, either inherited or caused by radiation, chemicals or viruses, eventually let the cell grow into a tumor.

3 More mutations may cause the cells to become malignant.

4 The malignant cells stop producing a chemical that prevents blood vessels from forming. New capillaries then grow into the tumor, providing it with nutrients. This also creates a route for malignant cells to break away from the main tumor mass and travel to other parts of the body, where they start new cancers.

5 Chemotherapy can kill the malignant cells, but if there is even one cancer cell that is resistant to the treatment, it will survive and grow into a new tumor. This new cancer will be impervious to the treatment.

liver-cancer patients. In the latter group, aflatoxin, a fungal contaminant of food, is the carcinogen, and it alters DNA in an exquisitely precise way, substituting in a single location a *T* (thymine) for a *G* (guanine) in DNA's four-letter chemical alphabet.

How can such a small mistake—the equivalent of changing the spelling of Smith to Smyth—have such an impact? Each three-letter "word" of a gene "sentence" spells out the instructions for producing 1 of 20 amino acids, compounds that in turn link to form proteins. A change in just one letter can result in the substitution of one amino acid for another. The new amino acid will be larger, smaller, stiffer or more elastic than the correct one. In ways radical and subtle, it will affect the shape of the protein and its activity. For if a cell is like a factory, then a protein is a cog in a machine that may have as many as 50 components. "If one of them develops a kink in its structure," says Harris, "then the machine doesn't fit together as well."

Kinks in proteins that form the nuclear matrix—a dynamic scaffold to which DNA is attached—may be particularly diabolical. The reason cancer cells typically have a swollen and misshapen nucleus, believes Johns Hopkins molecular biologist Donald Coffey, is that the proteins that form the nuclear matrix are misaligned in some fashion. Inside the matrix, notes Coffey, 50,000 to 100,000 loops of DNA are coiled like a Slinky, but the length of the loops, and where they begin and end, varies from tissue to tissue. The genes closest to the matrix are those that a particular cell intends to have turned on. Genes meant to stay inactive are much farther away. The conclusion is inescapable: a mutation in a gene that changes the architecture of the nuclear matrix could wreak havoc by turning the wrong genes on or off.

YEARNINGS FOR IMMORTALITY Normal cells do not live forever. Under certain circumstances, cells are actually programmed to die. One of the most fascinating features of early development, for example, is the explosive proliferation of certain types of cells, followed by mass suicide. Human embryos start with paddles for hands; it is cell death that gives them fingers. Neurons also expire by the billions as the brain refines its circuitry during development. In adults, the cell-death program serves as a stern disciplinarian. Cells that become irreparably damaged are expected to fall on their swords for the greater good of the organism. "For an animal to live," says Dr. Samuel Broder, director of the National Cancer Institute, "it must contain within its cells the knowledge that they have to die. But the cancer cell divides at all cost. It's forgotten how to die."

The tumor-suppressor gene p53 is often described as "the guardian of the genome" because it keeps watch over DNA during cell division. When damage occurs, p53 commands other genes to bring cell division to a halt. If repairs are made, then p53 allows the cell cycle to continue. But in some cases, if the damage is too serious to be patched, p53 activates other genes that cause the cell to self-destruct. Mutations in p53, which have been detected in more than 50% of all human cancers, are thus extremely dangerous. In laboratory cultures, some cancer cells that possess mutant versions of p53 do not die when challenged by antitumor agents, while those that have normal p53 genes go belly-up.

ROBERT HOLMGREN FOR TIME, BACKGROUND LOS ALAMOS NATIONAL LABORATORY

IMMORTALITY These glowing telomeres on chromosome tips act as molecular clocks. Calvin Harley has found how cancer cells stop the ticktock.

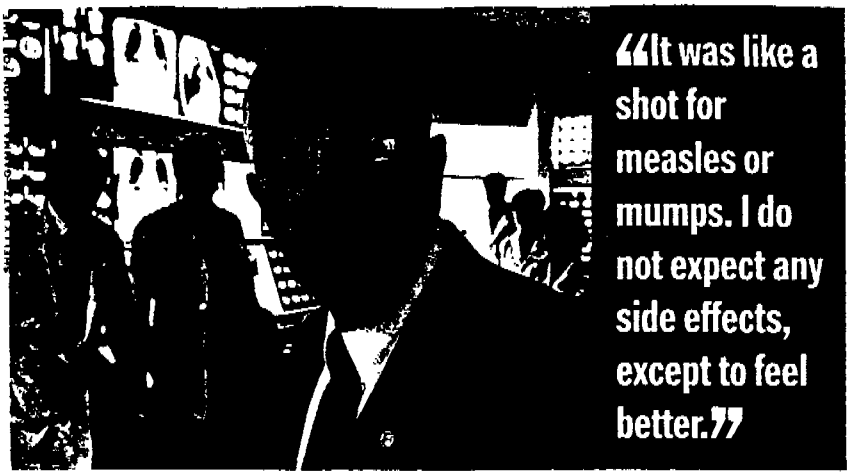
Healthy cells apparently have a precise system for ensuring their mortality; short strips of DNA known as telomeres seem to provide a molecular clock. When a cell is young, it has more than a thousand telomeres strung along the ends of chromosomes like beads in a necklace. Each time a cell divides, 10 to 20 telomeres are lost, and the necklace grows shorter. Eventually, after many cell divisions, the necklace becomes so short that the cell fails an internal health check designed to keep old, possibly damaged cells from reproducing. Result: cell division stops, the cell begins to age rapidly, and eventually it dies. Cancer cells, in contrast, have learned to stop the ticking of the telomere clock. According to research published last week in the *Proceedings of the National Academy of Sciences* by Calvin Harley and colleagues at McMaster University in Hamilton, Ontario, malignant cells foil the clock by producing an enzyme—telomerase—that protects the length of the telomere chains. In essence, telomerase makes the cancer cell immortal.

A CALL FOR BLOOD Perhaps the most critical stage in the life of a tumor comes after it expands to about a million cells. At this point, it is "much smaller than a BB," says Dr. Judah Folkman of Harvard Medical School. This tiny mass—known as a carcinoma in situ, literally cancer in place—is malignant, but not yet dangerous. Why? Because the cells at the center of the tumor are too far from the bloodstream to obtain essential nutrients, they are less vigorous. Like a society with zero population growth, a carcinoma in situ adds about as many new cells as it loses old ones.

Months, years, even decades may pass. Then an ominous transition occurs. Some cells in the tumor begin secreting chemicals that attract endothelial cells—the key components of blood vessels. These cells form capillaries that grow into the tumor. They also pump out molecular messengers called growth factors that stimulate the tumor to divide more quickly.

What triggers blood-vessel formation, or angiogenesis, as the process is known? A major factor, scientists believe, is a sudden drop in the cancer cell's production of thrombospondin, a protein that inhibits the growth of new blood vessels. In the normal adult, angiogenesis is not only a rare event, but one cells strive to prevent, save for special circumstances like wound healing. For blood vessels invading joints can cause arthritis, and those invading the retina of the eye can cause blindness. To prevent such damage, cells keep blood vessels at bay by pumping out thrombospondin. At a recent scientific conference, Noel Bouck, a molecular biologist from Northwestern University Medical School, stunned her colleagues by presenting preliminary data suggesting that thrombospondin production may be regulated by that ubiquitous gene, p53.

PULLING UP STAKES Angiogenesis is the harbinger of metastasis. The same vessels that feed the tumor also provide it with av-



JACK SWEPSTON, 48. Pancreatic Cancer. On March 31 this Dallas dentist traveled to the National Cancer Institute in Bethesda, Maryland, to receive a new type of anticancer vaccine. Prepared by a team of researchers, including Drs. David Carbone and John Minna of the University of Texas Southwestern Medical Center, the vaccine was a synthetic version of a mutant protein fragment found in Swepston's tumor. The hope is that the immune system will learn to recognize this target and destroy the cells that make it. "I haven't felt a significant improvement yet," he says, "but the doctors are tremendously excited."

enues of escape. Not all the myriad cells shed by tumors survive the turbulent voyage through the bloodstream, notes experimental oncologist Ann Chambers of the London Regional Cancer Centre in Ontario. But those that do eventually slip through blood-vessel walls with ease. Using a video camera attached to a microscopic lens, Chambers has watched in wonder as melanoma and breast-cancer cells, injected into mice, become lodged in capillary walls, then crawl out into the liver. Three days later, her camera resolves the spidery shapes of tiny metastatic growths. The lesson, Chambers believes, is depressingly clear. Cancer cells zip in and out of blood vessels so readily that, once angiogenesis occurs, they should be presumed to have already spread around the body.

Metastasis is an event of awesome complexity, one that requires multiple genes to cooperate as closely as musicians in an orchestra. Some of these genes code for chemical solvents that enable the advancing cell to dissolve surrounding tissue. Others order up the production of adhesion molecules that, like treads under a tank, move the cell forward. Why would genes do that? The answer, notes Patricia Steeg of the National Cancer Institute, is that while the genes important to metastasis are abnormally turned on, they are not necessarily abnormal themselves. A cancer cell, in many ways, is not that different from an embryonic cell on its way to becoming a patch of skin or a bundle of nerves. Both embryonic and cancer cells divide and form ill-defined clumps. Both get up and move around. Both migrate and populate new areas. But while an embryonic cell stops proliferating and matures into adult tissue, the cancer cells just keep dividing.

One reason for the difference may lie in a gene known as nm23, first identified by Steeg in 1988. It seems to help mature cells stop dividing and arrange themselves in an orderly fashion. Steeg's research suggests that in cancer cells this crucial gene often malfunctions. When she introduced a normal nm23 gene (nm stands for nonmetastatic) into highly malignant human breast cells, then injected these cells into mice, their tendency to form metastases dropped as much as 90%.

GUARDING THE MASTER SWITCH Until last week, p53, the subject of some 1,000 scientific papers in 1993 alone, was considered the most important cancer gene. The journal *Science* even named it Molecule of the Year. But now there is a new contender for notoriety—MTS1, as Alexander Kamb and his colleagues refer to the multiple tumor-suppressor gene they have just discovered. "Multiple" refers to the fact that defects in this gene can cause many kinds of cancer, including melanoma, lung, breast and brain tumors. In fact, functional copies of MTS1 may be missing in more than 50% of all human cancers.

What makes MTS1 so significant is its clear role in the cell-division cycle. A cell divides not at will but in response to specific signals, such as growth factors produced by white blood cells rushing to repair a wound. These signals are picked up by receptors on the membrane of the cell and passed along—like batons in a high-speed relay—through the interior, all the way to a master "on" switch positioned deep in the nucleus. Not surprisingly, many oncogenes, including one called ras, the first human cancer gene ever identified, are involved in this type of signaling pathway. But there are other molecules that determine whether the cell should heed these signals. And the small protein produced by

THE BIG KILLERS

Estimated deaths in U.S., 1994

		Deaths	New cases	Five-year survival rate	Risk factors
Lung		153,000	172,000	13%	Cigarette smoking; exposure to asbestos, chemicals, radiation, radon
Colon/Rectum		56,000	149,000	58%	[illegible]
Female Breast		46,000	182,000	79%	Age; family history; no pregnancies; late menopause; early menarche
Prostate		38,000	200,000	77%	[illegible]
Pancreas		25,900	27,000	3%	Age; smoking; fat intake
Lymphoma	Hodgkin's Non-Hodgkin's	22,750	52,900	78% 52%	[illegible]
Leukemia		19,100	28,600	38%	Genetic abnormalities; exposure to ionizing radiation, chemicals; viruses
Ovary		13,600	24,000	39%	[illegible]
Kidney		11,300	27,600	55%	Smoking
Bladder		10,600	51,200	79%	Smoking
Uterus	Cervical Endometrial	10,500	46,000	67% 83%	Intercourse at an early age; multiple sex partners; smoking Early menarche; late menopause; obesity
Oral		7,925	29,600	53%	Smoking, excessive use of alcohol
Skin Melanoma		6,900	32,000	84%	Sunburn; fair complexion; exposure to coal tar, pitch, creosote, arsenic, radium

Source: American Cancer Society

MTS1 appears to be among the most important inhibitors of cell division. Last year researchers at New York's Cold Spring Harbor Laboratory discovered that a protein they called p16 stifled an enzyme that is a growth promoter. Last week it became clear that p16 and the MTS1 protein are one and the same.

TARGETS FOR CANCER FIGHTERS Theoretically, any gene that goes awry in a cancer cell offers a way to attack the problem. But those that directly influence a cell's decision to divide are spurring particular interest. The protein made by the MTS1 gene seems exceptionally promising, for it has characteristics suggesting it may be easily fashioned into a drug, which then might be able to stop tumor cells in their tracks. "In terms of therapeutic potential," declares Kamb, "MTS1 may be the most important tumor-suppressor gene yet discovered."

Still, as pharmaceutical companies well know, many surprises can pop up on the way to developing a new drug, and other approaches to cancer therapy may win out in the end. Among the possibilities are anticancer vaccines designed to stimulate the immune system to combat tumors. Currently being tested in the U.S. and Canada is a vaccine that spurs an assault on the weirdly configured carbohydrates that protrude from tumor cells like spikes on a medieval ball and chain. At the meeting of the American Society for Cancer Research last week, Dr. David Berd of Thomas Jefferson University presented the most encouraging evidence to date that the vaccine strategy may work. Berd told of inoculating 47 melanoma patients with a vaccine made of their own tumor cells inactivated by radiation. Three years later, 60% remained tumor-free, compared with 20% in the unvaccinated control group. The approach works best, apparently, in patients who have tumors small enough to be surgically removed but whose disease shows signs of spread.

The discovery announced last week that cancer cells rely on the enzyme telomerase to stay alive opens up a different attack strategy. The leader of that research team, Calvin Harley, has taken a leave from McMaster University to work at Geron Corp. in Menlo Park, California. The company is trying to craft a drug that will block the action of telomerase. "The cancer cell," explains Harley, "is already very old. If we can inhibit telomerase, we might cause the tumor to die after a few doublings." Even better, the fact that cancer cells produce telomerase and that normal cells (save for sperm) don't, says Harley, "gives us hope that we may be able to develop a drug without serious side effects."

The formation of blood vessels in a tumor through angiogenesis is another promising target for an anticancer drug—because the process is so rare in normal cells. Clinical trials have begun on several compounds that interfere with angiogenesis. One such compound comes from a fungus that was accidentally discovered in 1989 when it contaminated cultures of endothelial cells in Judah Folkman's Harvard laboratory, dramatically curtailing their growth. This drug, says Folkman, is aimed not at curing cancer but at prolonging the period of time colonies of tumor cells missed by conventional therapy remain in place without spreading. "Suppose we prolong this period of dormancy for 10 years, and then another 10 years," muses Folkman. "Why, now we're beginning to compete with the normal life span."

Indeed, what seems most significant about all the new therapies, what joins them together, is not their power, for this has yet to be proved. Rather, it is the seismic shift in strategy they collectively represent. Increasingly, researchers speak not of slaughtering the cancer cell but of tricking it into dying naturally, perhaps of old age, as other cells do. They also talk of reining in the cancer cell, even rehabilitating it, a task that demands the development of less toxic drugs that can be tolerated over a lifetime. The model for cancer therapy of the future already exists. "After all, we don't cure diseases like diabetes and hypertension," says Dr. Lance Liotta, the National Cancer Institute's leading metastasis expert. "We control them. Why can't we look at cancer that way?"

By this reasoning, even metastatic cancer may eventually be brought to heel. Squeezed into a tiny cubicle day after day at the National Cancer Institute, Patricia Steeg stares at colonies of aggressive breast-cancer cells that have shut down the protective nm23 gene. Soon she will squirt over these colonies newly identified antitumor compounds. Among them she hopes to find one, maybe more, that interferes with metastatic growth. A total of 14 of these compounds are already sitting in a freezer in her lab—white crystals that cluster like snowflakes in the bottom of test tubes. If these fail to have an effect, Steeg has a list of more than 30 others that might. Like many cancer researchers, she conveys, through her own personal enthusiasm, a sense that an immense psychological barrier has been breached. No, Steeg has not yet found a drug that cures cancer or even controls it. But, she exclaims, "I'm beginning to like the odds." ■

ANN FAGAN, 37, Colorectal Cancer Ten years ago, when Ann Fagan, a paralegal from Conyngham, Pennsylvania, was found to have cancer, she underwent an ileostomy, a procedure that constructs an opening for the bowels through the abdominal wall. Last year tests revealed that her daughters Katie (left), 13, and Sarah, 11, had inherited a genetic defect that puts them at high risk for the same type of cancer. But this diagnosis has a silver lining, since the girls will be able to have surgery before rather than after cancer develops. Cancer susceptibilities that come from inherited mutations may account for 20% of all cases.