of a close spatial association of C4 with MLR determinants on the lymphoid cell surface. The existence of C4 in absence of MLR antigens on melanoma cells (unpublished results) indicates that C4 is not itself an MLR antigen. Alternatively, the MLR may require, in addition to differences in MLR antigens, other interactions or signals between the stimulating and responding cells. The C4, which in other systems functions as a ligand between complexes bearing C4 and lymphoid cells having C4 receptors, may operate equivalently in the MLR.

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References and Notes

1. G. Trinchieri, D. Bernoco, S. E. Curtoni, V. C. Miggiano, R. Ceppellini, in *Histocompatibility Testing 1972* (Munksgaard, Copenhagen, 1973), p. 509; V. C. Miggiano, D. Bernoco, J. Lightbody, G. Trinchieri, R. Ceppellini, *Transplant. Proc.* **4**, 231 (1972); V. P. Eijsvoogel, R. du Bois, C. J. M. Melief, W. P. Zeylemaker, L. Raat-Koning, L. de Groot-Kooy, *ibid.* **5**, 415 (1973).
2. P. Démant, J. Capková, E. Hinzová, B. Vorácová, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 863 (1973).
3. A. Ferreira and V. Nussenzweig, *J. Exp. Med.* **141**, 513 (1975).
4. J. B. Ziegler, C. A. Alper, H. Balner, *Nature (London)* **254**, 609 (1975).
5. S. M. Fu, H. G. Kunkel, H. P. Brusman, F. H. Aller, Jr., M. Fotino, *J. Exp. Med.* **140**, 1108 (1974); N. K. Day, P. L'Esperance, M. Siniscalco, R. A. Good, A. F. Michael, J. Hansen, B. Dupont, C. Jersild, *ibid.* **141**, 1464 (1975); S. M. Fu, R. Stern, H. G. Kunkel, B. Dupont, J. A. Hansen, N. K. Day, R. A. Good, C. Jersild, M. Fotino, *ibid.* **142**, 495 (1975).
6. F. H. Allen, *Vox Sang.* **27**, 382 (1974).
7. R. A. Lerner and L. D. Hodge, *J. Cell. Physiol.* **77**, 265 (1971).
8. M. A. Pellegrino, S. Ferrone, M. P. Dierich, R. A. Reisfeld, *Clin. Immunol. Immunopathol.* **3**, 324 (1974).
9. R. D. Schreiber and H. J. Müller-Eberhard, *J. Exp. Med.* **140**, 1324 (1974).
10. H. J. Müller-Eberhard and I. H. Lepow, *ibid.* **121**, 819 (1965).
11. S. H. Ohanian and T. Borsos, *J. Immunol.* **112**, 979 (1974).
12. S. Ferrone, M. A. Pellegrino, R. A. Reisfeld, *ibid.* **107**, 613 (1971).
13. S. Ferrone, A. Ting, M. A. Pellegrino, P. I. Terasaki, R. A. Reisfeld, *J. Clin. Invest.* **55**, 388 (1975); D. L. Mann, L. Abelson, S. Harris, D. B. Amos, *J. Exp. Med.* **142**, 84 (1975); R. J. Winchester, S. M. Fu, P. Wernet, H. G. Kunkel, B. Dupont, C. Jersild, *ibid.* **141**, 924 (1975).
14. M. A. Pellegrino, S. Ferrone, A. Pellegrino, in *Transplantation Antigens: Markers of Biological Individuality*, B. D. Kahan and R. A. Reisfeld, Eds. (Academic Press, New York, 1972), p. 433.
15. R. A. Reisfeld, M. A. Pellegrino, B. D. Kahan, *Science* **172**, 1134 (1971).
16. T. Meo, T. Krasteff, D. C. Shreffler, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 4536 (1975).
17. D. Saunders and M. Edidin, *J. Immunol.* **112**, 2210 (1974).
18. V. A. Bokisch and A. T. Sobel, *J. Exp. Med.* **140**, 1336 (1974); G. D. Ross and M. J. Polley, *ibid.* **141**, 1163 (1975).
19. R. J. Harzman, M. Segall, M. L. Bach, F. H. Bach, *Transplantation* **11**, 268 (1971).
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Drinking Water and Cancer Mortality in Louisiana

Abstract. *Multivariant regression analysis indicates a statistically significant relation between cancer mortality rates in Louisiana and drinking water obtained from the Mississippi River. This is true for total cancer, cancer of the urinary organs, and cancer of the gastrointestinal tract.*

There is a growing consensus that the majority of human cancers are caused by chemical carcinogens in the environment and, hence, that they are ultimately preventable (*1*). Although there has been considerable interest in the role of air and food in environmental carcinogenesis, there has been relatively little attention directed to the possibility that carcinogens in drinking water may be causally related to human cancers (*2, 3*). Several studies have demonstrated the presence of chemical carcinogens in river water (*4*) and in treated municipal drinking water (*5, 6*), and others have shown that carcinogens are introduced during chlorine treatment (*7*); the question remains whether or not their concentrations, generally at or below the parts-per-billion level, are sufficiently high to have detectable effects on cancer rates. In 1974 we reported a preliminary regression analysis on the possible link between drinking water and cancer (*8*); we now present further results.

Louisiana was studied because of (i) suspicions of the possible etiologic role of drinking water in the high incidence of bladder cancer in New Orleans (*9*), (ii) the identification of carcinogens in Mississippi River drinking water (*10*), and (iii) the disparity between the quality of Mississippi River drinking water and other sources in Louisiana. Out of a total 1960 population of 3.3 million, living in 64 parishes, 32 percent (representing part or all of the population in 11 parishes) were supplied drinking water from the Mississippi River (Table 1), 56 percent were supplied groundwater, and 12 percent were supplied from other surface water supplies. On the assumption that concentrations of carcinogens in Mississippi River water have historically been higher than those in other water supplies in Louisiana, we defined the drinking water variable (W) as the percent of the parish population drinking water from the Mississippi River or its distributaries (*11*). Other independent variables are rurality (R), income (I), and occupation. Urbanization and income were defined for whites and nonwhites separately, but the other independent variables were not since the data were unavailable. The occupational variables are the proportion of the total number of employees of each parish in 1962 employed in the petroleum and coal products industry (Pt), in the chemicals industry (C), and in the mining industry (M) (*12*).

Table 1. Louisiana parishes that receive drinking water from the Mississippi River, given as percentage of the population of each parish.

Parish	Percent
Ascension	28
Assumption	83
Jefferson	100
Lafourche	96
Orleans	100
Plaquemines	100
St. Bernard	100
St. Charles	100
St. James	77
St. John the Baptist	81
St. Mary	61

Dependent variables were age-adjusted, 20-year mortality rates (*13*) associated with cancers of the gastrointestinal and urinary tracts (*14*) and with total cancer. Had the numbers of mortalities been sufficiently high, disaggregation into time periods shorter than 20 years and into age groups would have been desirable. However, for several cancer sites the number of mortalities over all age groups and over the entire 20-year period was small (sometimes zero) for some parishes.

To compensate for the small numbers, related cancer sites were grouped: for urinary cancers, the rates for kidney, bladder, and other urinary organs were combined; for gastrointestinal cancers, the rates for stomach, large intestine (except rectum), and rectum were combined. Although combining mortality rates tends, through averaging, to decrease random error, a regression with total cancer as the dependent variable may be hard to interpret because cancers of unrelated organs behave differently. Two sites were chosen that could be expected to be less linked to drinking water than urinary and gastrointestinal organs and in which cancers are moderately common, the breast for females and the prostate for males.

Little was known about the true interaction of the independent and dependent variables; therefore, because it is often robust against specification error, the simplest model, a linear one, was chosen and estimated by least squares (*15*). The coefficient for the source of drinking water in the regressions for gastrointestinal cancer is significant ($P < .01$) for all four population groups (*16*) (Table 2); in the regressions for urinary cancer it is significant for white males and nonwhite females; in the regressions for total cancer, it is significant for white males, nonwhite males, and nonwhite females (*17*).

Rurality is also a strong variable in the sense that all of the regression coefficients have the anticipated sign, and many are significant. Income is not consistent in sign and is often insignificant. The occupational variables add little to the variance accounted for by the regression (R^2). However, only a small fraction of the total work force was in any of the three industries, and for each of the three industries, exposure to potential carcinogens may have varied widely from plant to plant and within a single plant. Occupational effects could exist but be "buried" in the aggregate data.

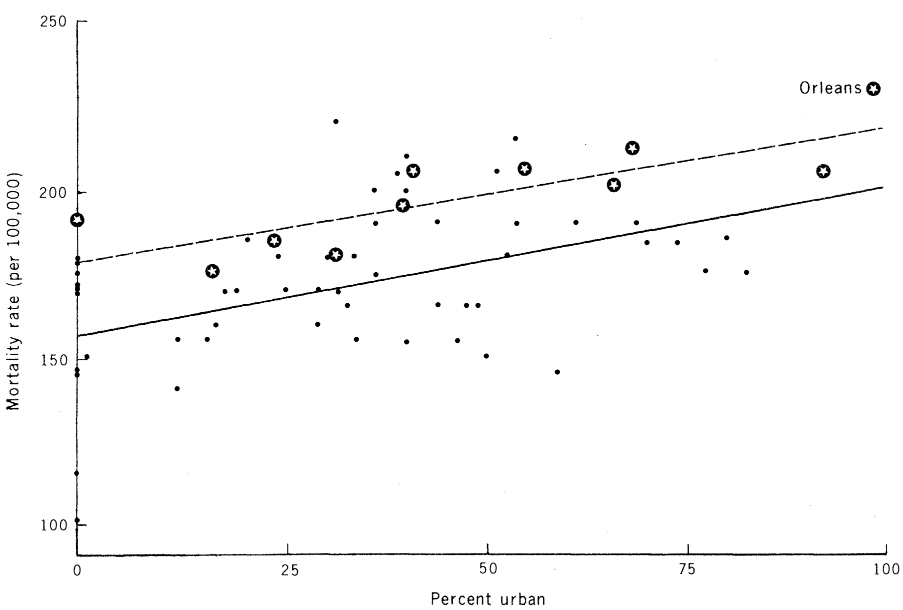

Fig. 1. Regressions of the total cancer rate for white males upon urbanization. Parishes without drinking water from the Mississippi (closed circles); parishes with some or all of their drinking water from the Mississippi (stars). The dashed line is the regression line for the 11 parishes using Mississippi water, and the solid line is the regression line for the 53 parishes not using Mississippi water.

Table 2. Summary of regression analysis. Mortality rate is the Louisiana mean cancer mortality rate (per 100,000); R^2 is the coefficient of determination. Abbreviations: W, the percentage of the parish population drinking water from the Mississippi River or its distributaries; R, the percentage rural; I, the median family income in thousands of dollars; Pt, the proportion of the total number of employees of each parish employed in the petroleum and coal products industry; C, the proportion employed in the chemicals industry; and M, the proportion employed in the mining industry.

Type of cancer	Mortality rate (per 100,000)	R^2	Regression coefficients on mortality rates of					
			W	R	I	Pt	C	M
Total cancer								
White male	190	.42	32.5†	−55.2†	−5.5*	−10.6	17.0	−.4
Nonwhite male	194	.37	49.5†	−0.6†	0.01	71.6	−43.2	9.6
White female	119	.10	3.0	−21.9*	−3.0			
Nonwhite female	114	.32	29.3†	−0.2*	0.005			
Urinary organs								
White male	11	.43	3.6†	−5.5†	−0.3	−21.7	16.7*	6.4
Nonwhite male	8	.18	1.6	−0.06*	−0.003	−31.4	14.2	−0.7
White female	4	.06	1.5	−0.5	−0.0			
Nonwhite female	5	.12	2.7*	−0.009	0.001			
Gastrointestinal organs								
White male	31	.39	7.0*	−14.8†	−1.9†	−19.3	27.5*	−10.3
Nonwhite male	47	.33	19.4†	−0.07	0.006	45.5	−18.3	−16.0
White female	23	.14	4.9*	−4.3	−0.8			
Nonwhite female	29	.30	13.3†	−0.08	0.002			
Prostate								
White male	18	.14	2.1	−6.7*	−1.3*	8.4	−0.3	4.6
Nonwhite male	29	.15	0.4	−0.006	0.006	−81.3	−17.6	−27.6
Breast								
White female	21	.31	0.96	−8.5†	0.4			
Nonwhite female	22	.07	4.2	−0.04	−0.001			

$^*P < .05$. $^†P < .005$.

A pattern of relative "protection" of white females against total cancers and those of urinary organs and the gastrointestinal tract can be seen in the mean mortality rate, in the R^2's, and in the values of t for drinking water. If there is no underlying relationship between drinking water and cancer, the pattern of the values of t for water source could be a chance phenomenon. But this explanation would not account for the pattern of low mean rates and R^2's for white females compared with other groups. On the other hand, a factor acting in part through or in conjunction with drinking water could help explain the pattern of all three statistics—the mean rates, the R^2's, and t for W.

Three possible sources of spurious correlation have been suggested. First, cancer rates in New Orleans might be inflated if cancer patients move to New Orleans and establish residence to take advantage of the availability of specialized or free medical care, and then die there. However, when we calculated the regressions for total cancer with New Orleans removed from the data, the coefficient on W remained positive and significant. (An indication of the role of New Orleans in the regressions can be seen in Fig. 1.) A second possible source of spurious correlation might arise with regional differences in diet or other socioeconomic variables, since parishes that receive drinking water from the Mississippi River are grouped in southern Louisiana. However, restricting the data to the 29 southern parishes that are suggested to be socioeconomically distinct from northern parishes (*18*) did not change the basic relations between the independent variables and cancer mortality rates. A third possible source of spurious correlation is that elevation might be an important omitted variable, on the ground that low-lying areas might be more subject to pollution (*19*). However, including elevation, which is negatively correlated with W, leaves W significant.

Although these three hypotheses do not explain away the role of W, there remain the problems of misspecification in the simple linear model and of omission of variables. For example, data on tobacco and alcohol consumption and air pollution by parish were unavailable. Although these exposures are in part reflected in the rurality and income variables, it would have been preferable to have included these variables explicitly. Moreover, the regression analysis cannot distinguish among organic chemicals and other possible carcinogens in Mississippi drinking water. A misspecification in the error structure arises from the fact that parishes vary in population. Heteroskedastic correction left the coefficients for drinking water roughly the same but raised the values of t by about 50 percent on average, leading to a large increase in the level of significance. While statistical studies cannot by themselves establish causality, this regression study supports the hypothesis that there is a link between carcinogens in drinking water and cancer mortality.

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References and Notes

1. *Prevention of Cancer* (Technical Report Series 276, World Health Organization, Geneva, 1964); E. Boyland, *Prog. Exp. Tumor Res.* **11**, 222 (1969); H. Higginson, *Can. Cancer Conf.* **8**, 40 (1969); S. S. Epstein, *Nature (London)* **228**, 816 (1970); *Cancer Res.* **34**, 2425 (1974).
2. P. Stocks, *Regional and Local Differences in Cancer Death Rates: Studies on Medical and Population Subjects* (General Registry Office, No. 1, London 1947); J. C. Diehl and S. W. Tromp, *First Report on the Geographical and Geological Distribution of Carcinoma in the Netherlands* (Foundation for the Study of Psychophysics, Leiden, Netherlands, 1953); S. W. Tromp, *Schweiz. Z. Pathol. Bukknol.* **18**, 929 (1955).
3. G. B. Cook and F. R. Watson, *Mo. Med.* **63**, 997 (December 1966).
4. K. A. Dostal, R. C. Pierson, D. G. Hager, G. G. Robeck, *J. Am. Water Works Assoc.* **57**, 663 (1965); *Organic Chemical Pollution of Freshwater: Water Quality Criteria Data Book* (Environmental Protection Agency, Washington, D.C., 1970), vol. 1; J. Friloux, *Petrochemical Wastes as a Pollution Problem in the Lower Mississippi River* (Environmental Protection Agency, Baton Rouge, La., 1971); R. A. Hites and K. Biemann, *Science* **178**, 158 (1972); H. J. Svec, J. S. Fritz, G. V. Calder, *Trace Soluble Organic Compounds in Potable Water Supplies* (Department of the Interior, Washington, D.C., December 1973).
5. W. C. Heuper and W. W. Payne, *Am. J. Clin. Pathol.* **39**, 475 (1963).
6. M. L. Schafer, J. T. Peeler, W. S. Gardner, J. E. Campbell, *Environ. Sci. Technol.* **3**, 1261 (1969); J. B. Andelman and M. J. Suess, *Bull. WHO* **43**, 479 (1970); *Industrial Pollution of the Lower Mississippi River in Lousiana* (Environmental Protection Agency, Dallas, Tex., 1972); R. D. Kleopfer and B. J. Fairless, *Environ. Sci. Technol.* **6**, 1036 (1972); R. Saunders, *J. Biomed. Mass Spectrom.* **1**, 209 (1974); M. Deinzer, R. Nelton, D. Mitchell, F. Kopfler, E. Coleman, *Trace Organic Contaminants in Drinking Water: Their Concentration by Reverse Osmosis* (Environmental Protection Agency, Cincinnati, Ohio, 1974); B. Dowty, D. Carlisle, J. L. Laseter, *Science* **187**, 75 (1975). These and other studies are summarized in G. A. Junk and S. E. Stanley [*Organics in Drinking Water*, Part 1, *Listing of Identified Chemicals* (National Technical Information Service, Springfield, Va., 1975)].
7. J. J. Rook, *J. Soc. Water Treat. Exam.* **23**, 234 (1974); T. A. Belar, J. J. Lichtenberg, R. C. Kroner, *The Occurrence of Organohalides in Chlorinated Drinking Water* (Environmental Protection Agency, Cincinnati, Ohio, 1974); B. J. Dowty, D. R. Carlisle, J. L. Laseter, *Environ. Sci. Technol.* **9**, 762 (1975).
8. R. H. Harris, *The Implications of Cancer-Causing Substances in Mississippi River Water* (Environmental Defense Fund, Washington, D.C., 1974).
9. L. J. Dunham, R. W. O'Gara, F. B. Taylor, *Am. J. Public Health* **57**, 2178 (1967).
10. "New Orleans Area Water Supply Study," draft analytical report (Environmental Protection Agency, Dallas, Tex., 1974).
11. There are large differences in the organic chemical content between ground and surface waters generally ["Preliminary Assessment of Suspected Carcinogens in Drinking Water," interim report to Congress (Environmental Protection Agency, Washington, D.C., 1975); *Preliminary Assessment of Suspected Carcinogens in Drinking Water* (Environmental Protection Agency, Washington, D.C., 1975); J. Symons, *J. Am. Water Works Assoc.* **67**, 634 (1975)]. The Mississippi system is a special case of surface waters, being far more heavily laden with organic chemicals than other sources of surface and ground water in Louisiana (J. L. Laseter, personal communication). Although it is difficult to estimate the industrial and agricultural emissions into the Mississippi several decades ago, chlorination has been practiced since the turn of the century and is of special importance in the Mississippi because of the relatively high concentration of organic matter naturally present. To construct W we used *1963 Inventory of Municipal Water Facilities* (Public Health Service Publ. No. 775, Department of Health, Education, and Welfare, Washington, D.C., 1964).
12. Abbreviations: R is the percentage of the parish population that is rural [for whites, R was taken from Bureau of the Census, *Census of Population: 1960* (Government Printing Office, Washington, D.C., 1963), vol. 1; for nonwhites, *ibid., 1950* (1952), vol. 2]; I is the median family income [for whites, I was taken from Bureau of the Census, *County and City Data Book: 1972* (Government Printing Office, Washington, D.C., 1973); for nonwhites, I was taken from Bureau of the Census, *Census of Population: 1950* (Government Printing Office, Washington, D.C., 1952), vol. 2]; Pt, C, and M were taken from total employment and industry employments [Bureau of the Census, *County Business Patterns, First Quarter: 1962* (Government Printing Office, Washington, D.C., 1963)].
13. T. J. Mason and F. W. McKay, *U.S. Cancer Mortality by County: 1950–1969* (Government Printing Office, Washington, D.C., 1974).
14. There is some suspicion that cancers of the urinary tracts are associated with polluted drinking water (*5, 9*).
15. We estimated the following two equations:
$$MRF_i = a_0 + a_1W_i + a_2R_i + a_3I_i + e_i$$
$$MRM = a_0 + a_1W_i + a_2R_i + a_3I_i + a_4P_i + a_5C_i + a_6M_i + e_i$$
where e_i is an error term; MRF_i is the age-adjusted mortality rate for some cancer site for females in parish i; MRM_i is the term for males.
16. Considered separately, the regression coefficient for drinking water is significant ($P < .05$) for kidney cancer, white males; for bladder cancer, white males and nonwhite females; for cancer of the rectum, white males and nonwhite males; for cancer of the stomach, nonwhite males and nonwhite females; and for cancer of the large intestine, white females. The coefficient for W in the first regression can be interpreted as follows. On the assumption that the underlying specification is correct, if a parish that has been entirely dependent on Mississippi River water ($W = 1$) were to switch entirely to groundwater ($W = 0$), it could expect in the long run to reduce its total cancer mortality rate for white males by 32.5 per 100,000. Since the mean total mortality rate for white males is 190 per 100,000 for all parishes, this would result in about a 17 percent reduction. Similarly, for nonwhite males and nonwhite females the reductions would be 28 and 22 percent, respectively. (The coefficient for white females is not significant.)
17. The significance of the coefficient for drinking water in the total cancer regressions does not depend on the inclusion of urinary and gastrointestinal cancers in total cancer; regressions with the dependent variable "all cancers except urinary and gastrointestinal cancers" have the same pattern of significance for the drinking water coefficient as regressions with total cancer.
18. T. A. DeRouen and J. E. Diem, "Ethnic, geographical differences in cancer mortality in Louisiana," 1975, unpublished report. This study also shows an association between parishes that drink from the Mississippi River and gastrointestinal cancers.
19. R. A. Tarone and J. J. Gart, unpublished review of (*8*), National Cancer Institute, with a reply from T. Page and R. H. Harris.

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Barium in Southern California Coastal Waters: A Potential Indicator of Marine Drilling Contamination

Abstract. *The present barium content of Southern California coastal waters was determined to be 11 to 22 micrograms per kilogram of seawater. These values may be used as base-line concentrations to monitor marine contamination during future offshore oil and gas explorations.*

Earlier analyses of the barium content of seawater revealed only the upper limit of the concentration (*1*). Recent results demonstrate that the barium content of open oceans increases with the depth of the water. The Pacific waters display barium concentrations of from 3 to 51 μg per kilogram of seawater (*2, 3*), whereas barium in the Atlantic waters ranges up to 105 μg/kg (*4*).

Table 1. Isotopic composition of common and spike barium (in units of atom percentages).

Component	Isotopic mass						
	130	132	134	135	136	137	138
Common barium	0.10	0.10	2.42	6.59	7.81	11.32	71.66
Spike barium							
Scripps	<0.001	<0.005	0.454	93.47	1.629	0.885	3.560
Oak Ridge	<0.1	<0.1	0.36	93.6	1.61	0.87	3.56