linking, we hydrolyzed the beads (6*N* HCl, for 24 hours at 110°C) and examined the resulting amino acid composition. A progressive increase in the number of modified lysine residues (21, 33, 44, and 47) was found as the concentration of glutaraldehyde was increased (1, 2, 3, and 4 percent, respectively). Although the rate of release could be controlled by varying the density of the matrix, only the 1 percent glutaraldehyde–cross-linked beads were susceptible to chymotrypsin digestion, an indication of their biodegradability. The other three systems were resistant to proteolytic destabilization even after prolonged incubation (days) with fresh enzyme. However, even with the lowest concentration of glutaraldehyde, the rate of release is at least ten times slower than that of unentrapped drug.

A wide range of compounds with different chemical and physical properties can be entrapped in the serum albumin matrix. These include water-soluble dyes (for example, methyl orange); morphine and its antagonist, naloxone; peptides; and proteins. This versatility stems from the mild conditions required for formation of beads under which most biologically active molecules are stable.

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Brain Tumors in Children and Occupational Exposure of Parents

Abstract. *Ninety-two cases of brain tumor in children less than 10 years old were compared with 92 matched controls for parental occupational history. Cases were more likely than controls to show maternal occupations involving chemical exposure, paternal occupations involving solvents, and employment of father in the aircraft industry. These three factors were not affected by adjustment for the potential confounding variables examined in this study.*

The issue of whether occupational exposures of parents cause malignant disease in offspring has been gaining attention. The results of five studies (*1–5*) that we reviewed, in which different populations, different techniques, and different age groups were used, are not consistent.

We investigated the possibility that parents of children with brain tumors are more likely to have had occupational exposure to chemicals than are parents of controls. Cases of brain tumors in children less than 10 years of age at diagnosis, identified from 1972 to 1977 by the Los Angeles County Cancer Surveillance Program (CSP) (*6*), were selected for study. A control was identified by an algorithm that matched patients by sex, race, and year of birth (within 3 years). Social class was matched by first attempting to locate a control among friends of the case (57 such controls were found) and, if no friend was available, by selecting a matching neighbor (35 controls). Mothers of 98 cases (84 percent of available mothers) and 92 controls (86 percent of first-match friends and 80 percent of first-match neighbors) were interviewed by telephone. The 92 matching pairs were analyzed.

Information sought about the mother included the work history during the year before pregnancy, during the three trimesters of pregnancy, during nursing, and at the time of diagnosis of the case. This included information on job title, actual job, name of employer, and what the company made or did. Other questions concerned whether protective equipment or clothing was used; whether chemical solvents, dust, or other fumes were inhaled; whether chemicals, solvents, oils, dust, and so forth, got on clothes or skin; and whether radiation or radioactive material was used. Each mother was asked similar questions about the job experiences of the child's father before conception, during the pregnancy, and at the time of diagnosis of the case. Information was also collected about the mother's smoking habits and use of drugs, alcohol, hair dyes, and certain foods during the pregnancy. Statistical analysis was done by standard matched-pair methods (*7–8*); pairs in which either the mother of a case or the control mother did not answer the relevant question were eliminated. All statistical significance levels are based on one-sided tests.

Questions about chemical exposure were more often answered in the affirmative by mothers of cases than of controls (Table 1). Mothers of cases reported skin exposure to chemicals more than three times as frequently as mothers of controls—relative risk (*RR*) 3.3—and that they inhaled chemicals, fumes, and dusts more often (*RR* = 3.0). To pursue the question of fathers' exposure to chemicals, all jobs and exposures mentioned for fathers of cases and of controls were listed and enumerated. Exposure to solvents (*RR* = 2.8), paints in particular (*RR* = 7.0), was more frequent for fa-

Table 1. Matched-pair comparison of parental occupational exposure of cases and controls. The mother was considered to have been exposed if exposed at any time from 1 year before conception through lactation. The father was considered to have been exposed if exposed during that period or at the time of diagnosis of a case.

Factor	Concordant pairs: both exposed	Discordant pairs		Relative risk	One-sided test (*P*)
		Cases exposed	Controls exposed		
	Mother				
Got chemicals on skin	0	10	3	3.3	.05
Inhaled chemicals or fumes	1	12	4	3.0	.04
One or both of the above	1	14	5	2.8	.03
	Father				
Exposed to chemical solvents	3	17	6	2.8	.02
Exposed to paints	0	7	1	7.0	.04
Worked in aircraft industry	2	10	0	∞	.001

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Table 2. Occupational information on parents of cases and controls who worked in the aircraft industry.

Diagnosis	Child's age	Mother's occupation	Father's occupation	Exposure
Astrocytoma	9	Wire soldering*†	Electronics assembler*†‡	Solder
Oligodendroglioma	8		Machinist*†‡	Trichloroethylene
Astrocytoma	6		Machinist*†‡	Dust, oils
Astrocytoma	7		Production scheduling and parts inspection*†	Trichloroethylene, methyl ethyl ketone
Medulloblastoma	4		Electrical engineer*†‡	
Glioma	4	Secretary*		
Astrocytoma	4	Keypunch operator*†	Computer operator*†‡	
Medulloblastoma	< 1		Scientist-physicist*†‡	Ionizing radiation (wore film badge)
Astrocytoma	< 1		Plane painter*†‡	Spray paint
Astrocytoma	9		Engineer‡	
Astrocytoma	8		Wing parts inspector*†	
Medulloblastoma§	4	Stockroom clerk*†		Dust, exhaust
Control		Secretary*†		
Medulloblastoma§	3		Flight line mechanic*†‡	Exhaust
Control			Electrical engineer*†‡	
Medulloblastoma§	< 1		Student-aircraft mechanic school*†‡	
Control		Secretary*	Technician-student*†‡	

*Occupation at any time during the year before pregnancy. †Occupation at any time during the pregnancy. ‡Occupation at time of diagnosis. §A parent of the case and matched control both had a history of employment in the aircraft industry.

thers of cases (Table 1). The increased risk to the child of brain tumor from the mother's exposure to chemicals cannot be explained by the father's exposure to solvents. The elevated risk to the child from the father's exposure to solvents during the pregnancy was only slightly reduced after adjusting for the mother's exposure.

A strong association was found between paternal employment in the aircraft industry and cases of brain tumor (see Table 2). Twelve fathers of cases worked in the aircraft industry either during the time of the pregnancy or at the time of diagnosis; only two fathers of controls had been employed in this industry, and both were matched to cases whose fathers also worked in the aircraft industry ($RR = \infty$, $P = .001$).

Our questionnaire on specific exposures in the aircraft industry provided limited information (Table 2). Trichloroethylene was mentioned twice by fathers of cases, and two fathers of cases were machinists, but there were no other clues to possible causes of the increased risk.

The three independent risk factors identified by this study—mother's exposure to chemicals, father's exposure to solvents (paints and others), and father's employment in the aircraft industry—were not significantly affected by possible confounding variables such as patterns of food consumption, drug use, alcohol use, and smoking habits.

Occupational exposure to chemicals by parents of cases may have been overreported. It is possible that the mother of a child with a brain tumor might recall more episodes of exposure than a mother of a control or that the interviewer might probe harder when interviewing case mothers, even though the interviewer was taught to ask questions in a standardized manner. However, mothers of cases were twice as likely to have worked during the year before pregnancy ($P = .02$), a result that is very unlikely to be due to bias. Also, information on where (which industry) the mother and father worked is unlikely to be biased.

The mechanism by which maternal exposure during pregnancy could result in adverse effects to a child seems evident. Several mechanisms by which the child could be affected by paternal exposure seem plausible: gonadal effects in the father that could be transmitted genetically to the child; exposure of the mother before pregnancy, during pregnancy, and during lactation from soiled clothing brought home from the father's workplace; or direct exposure of the child from soiled clothing.

The lack of detail of our occupational histories plus a general ignorance about the etiology of brain tumors prevents us from speculating about specific carcinogens that could account for our findings. On the basis of studies of both humans and animals there are several reasons to be concerned about occupational exposures to chemicals. In man, vinyl chloride (*9*) appears to be related to an excess in the incidence of brain cancer, and a cluster of glioblastoma has been reported in workers in a large petrochemical complex (*10*). Swedish chemists have also been reported to have an excess of gliomas (*11*). Some *N*-nitroso and nitrite compounds cause tumors in the nervous systems of animals (*12–15*); many of these compounds are found in industry (*16*). An association has been noted between the occurrence of meningioma in women and consumption of meats that contain high levels of nitrite (*17*), a precursor of *N*-nitroso compounds.

The CSP reports brain tumors in individuals of all ages and registration of incident cases in Los Angeles County involves a notation of occupation and employer at the time of diagnosis. We looked at all brain tumors in white men 25 to 64 years of age that were diagnosed between 1972 and 1976. There were 73 cases of brain tumors in men employed in the aircraft industry, an excess of 23 over the expected value, giving a proportional incidence ratio of 146. Whether a common exposure accounts for both the childhood and adult brain tumors is not known at this point.

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The Diaphragm: Two Muscles

Abstract. *The costal and crural parts of the diaphragm were separately stimulated in anesthetized dogs. Stimulation of the costal part increased the dimensions of the lower rib cage, whereas stimulation of the crural part decreased the dimensions of the lower rib cage. It is concluded that the diaphragm consists of two muscles that act differently on the rib cage.*

The action of the diaphragm on the chest wall has been a source of interest to physiologists for centuries (*1*). When the diaphragm contracts, it pushes down on the viscera and displaces the abdomen outward. However, the mechanical link between the diaphragm and the rib cage remains poorly understood (*2*) and is a subject of active research because of the importance of this muscle (*3*).

Traditionally, the diaphragm has been thought to use the abdominal contents as a fulcrum to expand the rib cage (*1*, *2*). A recent quantitative description of this old idea suggests that the diaphragm can lift and expand the rib cage only to the extent that abdominal pressure increases (*4*). Thus, the proposed link between the diaphragm and the intercostal and accessory muscles of inspiration is that these two muscle groups, as pressure generators, operate on the rib cage as though they were arranged in series (*4*). However, recent observations in man, coupled with mathematical considerations, suggest that the diaphragm acts partly in series and partly in parallel with the rib cage (*5*). The present report demonstrates that this is indeed the case in the dog and, further, that these different actions of the diaphragm on the rib cage correspond to anatomically distinct parts of the muscle.

The studies were performed on supine dogs anesthetized with Nembutal (25 mg/kg), intubated, and maintained under deep general anesthesia with supplementary doses. The abdomen was opened and stimulating electrodes were implanted in the abdominal side of the diaphragm—two pairs in the costal part bilaterally and two pairs in the crural part bilaterally. They were placed as close as possible to the central tendon to avoid stimulation of other muscles. The abdomen was closed and the electrodes were connected to two Disa stimulators (Disamatic, Inc.) so that we could separately stimulate the costal and crural parts. The stimulating pulses were square waves 0.2 msec in duration and 20 to 100 Hz in frequency; the number of muscle fibers activated was set by progressively increasing the voltage. We measured air flow and volume at the animal's mouth with a Fleisch pneumotachograph. Transabdominal pressure was measured as the difference between the abdominal and atmospheric pressures. Changes in lower rib cage and abdominal dimensions were determined by induction plethysmography (*6*).

Representative records are shown in Fig. 1. Electrical stimulation of the costal part of the diaphragm resulted in increases in lung volume and abdominal pressure and in outward displacement of the abdomen and lower rib cage; expansion of the lower rib cage increased as the stimulation became stronger. On the other hand, stimulation of the crural part, while also producing increases in lung volume, abdominal pressure, and abdominal dimensions, had no effect on lower rib cage dimensions. This was true for any amplitude of stimulation. Similar records were obtained for all the dogs studied.

In order to suppress the role played by the increase in abdominal pressure on the changes in rib cage dimensions, we repeated the procedure with the abdomen opened. Stimulation of the costal part of the diaphragm still displaced the rib cage outward, although less markedly than with the abdomen closed. By contrast, stimulation of the crural part re-

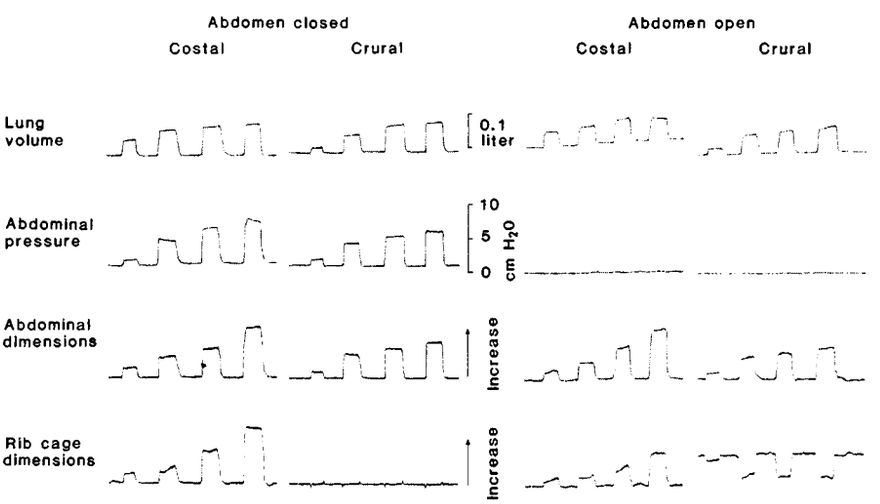

Fig. 1. Effect of stimulating the costal and crural parts of the diaphragm on lung volume, abdominal pressure, and abdominal and rib cage dimensions. The stimulation frequency was 100 Hz, and in each panel the voltage of the stimulation increased from left to right.

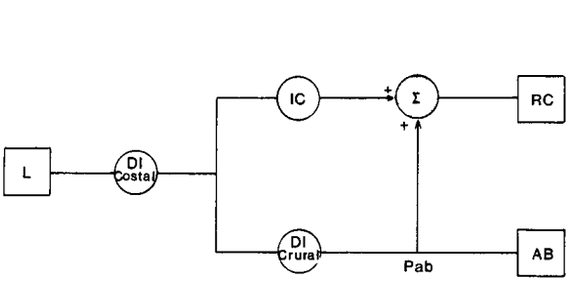

Fig. 2. Schematic diagram of the muscular control of the respiratory system. The squares represent structures (*L*, lungs; *RC*, rib cage; *AB*, abdomen) which are displaced by muscles, represented as circles (*DI*, diaphragm; *IC*, intercostal and accessory muscles of inspiration). Σ is a summing junction; *Pab* is the change in abdominal pressure resulting from diaphragmatic contraction.

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