

How Environmental Hazards in Childhood Have Been Discovered: Carcinogens, Teratogens, Neurotoxicants, and Others

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ABSTRACT. Review of the literature reveals that environmental hazards cause adverse health effects that include sterility, infertility, embryotoxicity, low birth weight, skin lesions, neurodevelopmental defects, immunologic disorders, cancer, and fear of late effects. They have been identified mostly by astute practitioners but also by a bacteriologist, an animal experimentalist, 5 factory workers in childless marriages, and a tipsy bystander in an economically impoverished area of Baltimore. Dust on a parent's work clothes has transported a hazard at work to a hazard at home (lead, asbestos, and chlordecone). Causality is established by showing a dose-response effect and reproducing the effect in studies of other exposed groups or by using another epidemiologic method, eg, prospective instead of retrospective study. Also, the findings should be biologically plausible and not attributable to a concomitant variable such as cigarette smoking. Contrary to front-page newspaper headlines, incidence rates for childhood leukemia are not rising. Preserving specimens for future studies has been valuable: blood from people who were exposed to dioxin in Seveso, Italy; mummified umbilical cords containing methyl mercury at Minamata Bay, Japan; and Guthrie dried blood spots to screen retrospectively for 43 genetic disorders and a specific prenatal cytogenetic abnormality in some children with 1 form of leukemia. Recommendations are given for enhancing interest in environmental hazards and their discovery by clinicians. *Pediatrics* 2004;113:945-951; case reports, case series, epidemiology, disease clusters, causality.

ABBREVIATIONS. AAP, American Academy of Pediatrics; PCB, polychlorinated biphenyl; DDT, dichlorodiphenyltrichloroethane; HCP, hexachlorophene; CDC, Centers for Disease Control and Prevention; ALL, acute lymphocytic leukemia.

Environmental hazards are usually first described by astute clinicians. The descriptions that follow are in part from personal experience beginning in medical school (radiation-induced teratogenesis), from conferences on the subject, records of Congressional testimony, books that are long out of print, and other literature on the first reports of specific hazards. Follow-up information on individual studies was obtained from the Internet. The history of teratogenesis as a result of drugs, although fascinating, is not covered here.

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FROM A SINGLE CASE

Soon after Kenneth W. Feldman opened his pediatric practice in Seattle, he treated a 32-month-old child for scald burns of the feet, sustained when the mother put the girl into the bath feet first. Starting with this single observation in 1978, Dr Feldman assembled a case series from local hospital records and went from house to house—57 of them—measuring the bath water temperature as it came from the tap. He found that the temperature, preset by the manufacturer, was usually 65°C (150°F), too high for the young child's tender skin. He mobilized support for legislation, which took effect in July 1983; it required new water heaters to be preset at 49°C (120°F).¹ Other states followed this example. His action protected children from these injuries,² which had generated an estimated 3000 emergency department visits and 300 hospital admissions annually in the United States.¹ The sequence of events went from a single case to a case series and then to legislative action. Dr Feldman received the American Academy of Pediatrics (AAP) Practitioner Research Award in 1991.

PHYSICAL AGENTS

Ionizing Radiation

In the 1920s, case reports were published about newborn infants with small head size and mental retardation after maternal exposure to radiotherapy early in pregnancy. In 1928, Douglas Power Murphy,³ a professor of obstetrics at the University of Pennsylvania, searched the literature and found 14 cases. By a mail questionnaire to other hospitals, he found 16 more.⁴ Among the children who were exposed in utero to the atomic bombs in Hiroshima and Nagasaki, a dose-response effect was found beginning at 60 cGy (60 rad) for mental retardation⁵ and at 20 cGy for small head size.⁶ Here individual clinical observations led to an epidemiologic study.

Another effect of x-irradiation was seen in children with ataxia-telangiectasia. They have a high frequency of lymphoma and when treated with conventional doses of radiotherapy have died of acute radiation sickness. After 2 case reports were published, a third case was seen by Jill Mann in Birmingham, UK, who consulted laboratory scientists. They found that fibroblasts in culture from this child had diminished survival after radiation exposure,⁷ later shown to be attributable to a DNA repair defect.⁸ Here, a pediatrician consulted cell biologists. (When lymphoma occurs early in childhood, pediatricians must be

aware that ataxia-telangiectasia may go undiagnosed because ataxia is not apparent until the child learns to walk, and telangiectasia of the conjunctivae does not appear until approximately 6 years of age.⁷)

Exposure to the Sun

The incidence of melanoma keeps climbing as a result of increasing exposure to ultraviolet light. In Scotland, the annual incidence has risen from 3.5 in 1979 to 10.6 per 100 000 in 1998 for men and 7.0 to 13.1 for women.⁹ Sun exposures in childhood and adolescence contribute substantially to the increase, as shown by epidemiologic studies.¹⁰

Children with xeroderma pigmentosum are especially sensitive to the sun. The reason was discovered by a bacteriologist, James E. Cleaver. He was on a streetcar in San Francisco reading a news article about a family whose children could go out of the house only at night because they were so sensitive to the sun. Cleaver was studying a strain of bacteria with sensitivity to ultraviolet light as a result of a DNA repair defect. He consulted pediatricians who located a family with xeroderma pigmentosum, and Cleaver found that they had the same DNA repair defect.¹¹ Here an observation from the laboratory was key to finding the human counterpart.

Asbestos

C.A. Sleggs, a physician in South Africa, encountered in his practice 3 patients with mesothelioma. He increased his series to 16 cases and found that they were in diverse occupations, but their histories revealed a feature in common. As children, they had lived downwind from open-pit asbestos mines.¹² The carcinogenicity of asbestos is related to its physical properties (length and diameter of the fibers) and could not have been predicted from its chemical structure.¹³ This research, which began with clinical observations, opened a large area of study for epidemiologists and laboratory scientists.

Children were exposed to asbestos insulation from schoolroom ceilings in buildings constructed just after World War II. No rise in mesothelioma incidence has been reported, but when exposure was high enough, it could happen. Frederick P. Li¹⁴ reported mesothelioma in a child and his mother 30 years after the child's diapers were made from cotton cloth that had been wrapped around asbestos. It was brought home from work by the father. This observation illustrates that exposures very early in life can cause cancer in adulthood.

CHEMICAL AGENTS

Tobacco

Nothing more need be said about cigarette smoking, so well known are its effects. Chewing tobacco is another matter. Teenage athletes may be heavy users, as they emulate their professional role models. The damage to their oral tissues can be severe, and cancer may be induced, as revealed by case reports and epidemiologic studies.¹⁵

Lead

Known since Hippocrates observed colic in lead miners, so much has been written about lead¹⁶ that here only some remarkable cases solved by astute observers are described. In the early 1930s, there was an outbreak of lead poisoning among children in an economically depressed area of Baltimore. An intern, Miriam E. Brailey, visited a home there to seek the source of the lead. She had no success until a bystander, Melrose Easter, whose "breath was strong with whisky," said that he thought burning of battery casings was the cause, for "the smell was bad, even made the food taste bad."¹⁷ Not only were the children affected but also the mother. In Raleigh, North Carolina, 48 years later, another family was affected by lead in batteries.¹⁸ Women who were employed at the battery factory wore their work clothes home, where the dust caused lead poisoning in their children.¹⁹ The report of these cases was accompanied by an editorial by J. Julian Chisolm, "Fouling One's Own Nest."²⁰—not only with lead but also with chlordecone (Kepone)²¹ and asbestos.¹⁴

Methyl Mercury

In the 1950s, an outbreak of a severe neurologic disorder occurred around Minamata Bay in Kyushu, Japan. It was traced to fish that were contaminated with methyl mercury, an industrial catalyst that was flushed into the bay. Birds, cats, and people who ate the fish were affected.²² An epidemic of cerebral palsy in children escaped notice until 1960; 40 cases were described before fishing in the bay was forbidden.²³ A cluster of people with strange behavior had occurred before the war in the same area, and to determine whether it, too, was attributable to methyl mercury, a study was made in 1975 of mummified umbilical cords, traditionally saved by Japanese.²⁴ The results showed that the outbreak could be traced back to 1928.²⁵ The lesson here is that when an environmental disease affects adults, one should look for an effect in infants who are born soon after.

Polychlorinated Biphenyls

In 1968, an epidemic of chloracne occurred in Kyushu, Japan. Its cause was quickly found: during the manufacture of cooking oil, pinhole erosions had developed in pipes that carried polychlorinated biphenyls (PCBs), a heat-transfer agent that cooled the oil. Approximately 2000 people were affected with Yusho (oil disease),²⁶ as were 7 liveborn infants who had "cola-colored" skin and were small for date. These intrauterine effects were reported in a journal with a small circulation,²⁷ so they did not become known outside Japan until a commentary appeared in *Teratology* in 1971.²⁸ A second episode occurred in Taiwan in 1979, in which approximately 2000 people developed chloracne and 39 newborn infants had hyperpigmentation.²⁹ In a case-control study, 117 children who were exposed in utero during or after maternal ingestion of the oil were compared with older siblings who were born before the episode. The exposed children had more abnormalities of the gingiva, skin (hyperpigmentation), nails, and teeth,³⁰

and in a study at 6 and 7 years of age³¹ they scored on average 5 points lower on 2 tests of cognitive development. The PCBs to which they had been exposed were thermally degraded and thus contaminated with polychlorinated dibenzofurans, which are very toxic. Some children were poisoned in utero long after maternal exposure, from the heat-degraded PCBs when they were mobilized from her body fat. Rogan et al³² reported that organohalides, such as PCBs and dichlorodiphenyltrichloroethane (DDT), are excreted primarily in breast milk. PCBs are a problem in the upper Hudson River, where they were dumped from old transformers and other electrical equipment, in which they were used as insulating fluids. A New York State Department of Health fish advisory³³ cautions women of childbearing age and children under 15 not to eat fish from the Hudson River south of Hudson Falls. The river is to be dredged to remove the PCBs.

Hexachlorophene, Experimental Rats

Hexachlorophene (HCP), an excellent antibacterial agent, was very widely used as a rinse for the skin of newborn infants from the 1950s to 1973. In 1970, at a site visit to Renate Kimbrough at the Centers for Disease Control and Prevention (CDC), a member of my staff learned that she had just produced spongiform lesions in the brains of rats by exposing them to HCP.³⁴ This raised a question about the safety of neonatal rinses, which was referred to AAP's Committee on Environmental Hazards. Laurence Finberg, a committee member, collected cord blood and samples of blood from newborns just before discharge from the hospital and found that they had up to two thirds of the toxic level in rats.³⁵ There was considerable opposition to discontinuing this effective antibacterial agent. The risk was no longer in doubt when, in 1972, 204 children in Paris, aged 3 months to 3 years, developed severe diaper rash and neurologic abnormalities after use of an infant powder that accidentally contained 6.3% HCP when there was supposed to be none. Thirty-six children died. The talc was prepared in the same area that HCP was kept, and 38 kg of HCP contaminated 600 kg of infant powder that went into 2898 cans.³⁶ Here again, a laboratory study pointed the way.

Chlordecone (Kepone)

Workers at a renovated gas station in Hopewell, VA, where chlordecone was made for 16 months, experienced tremors and other neurologic disturbances. They believed that the disease was attributable to the pesticide. One practitioner, more receptive than others to their complaint, sent a blood sample for study by the CDC, where a high level of chlordecone was found. This history illustrates the value of asking the patient what may have caused the illness. The men wore their contaminated work clothes home, and of 32 family members studied, 30 had chlordecone in their blood.²¹

Dibromochloropropane

In 1977, several workers in the manufacture of dibromochloropropane, a pesticide, noted that they

had not been able to father children. They thought that their exposure at work was the reason, but their physicians thought not. Five of the men brought their semen specimens to a local laboratory, which declined to give them the results. The laboratory agreed to send the information to a nearby university scientist, who was a consultant to the union and the company.³⁷ Epidemiologic studies were then made, 6 in the United States and 1 in Israel. Among 485 men who were occupationally exposed to dibromochloropropane, 12.8% were azoospermic and 22.1% were oligospermic.³⁸ In this instance, the patients not only identified the exposure but also arranged for laboratory confirmation.

Ethyl Alcohol

An array of congenital malformations in children of heavily alcoholic mothers were described by a French group in 1968 and independently recognized by a resident physician, Christy Ulleland, in Seattle the following year (reviewed by Streissguth³⁹). Jones and Smith⁴⁰ reported 8 Seattle cases in 1973. Among the findings are mental retardation, microcephaly, short palpebral fissures, and intrauterine and postnatal growth retardation. Epidemiologic studies have shown the frequency of fetal alcohol syndrome to be 1 in 1000 livebirths; a milder form, fetal alcohol spectrum disorders of learning and other cerebra-tion, affected an estimated 7 per 1000 in Seattle,⁴¹ surely the most common behavioral teratogen. Streissguth has devoted her career to expanding information on a major public health problem.

RESEARCH IN CLINICAL PRACTICE

Jonathon Rees,⁴² a Scottish dermatologist, has recently written in *Science* that as basic research has flourished, clinical breakthroughs have become less common. He was referring to observations such as those described above, when he wrote, "Most of the key insights . . . came from clinical investigators with a history of success in more than one field. One advance may be luck; two advances suggest something special." Most of these advances were substantial.

In thinking of how this might apply to pediatric practice, consider the career of William B. Wadlington of Nashville, TN, who regularly found patients of special interest in his practice. When he came upon such a patient, he reviewed the relevant literature and focused on how this patient or series of patients added to knowledge of the disease. He then recruited an academic pediatrician as a collaborator when necessary. In this way, in 30 years of practice, he published 30 papers. The subjects included an outbreak of erythema infectiosum, which he was the first to recognize in the area, an unusual form of kernicterus, studies of propionic acidemia, heat stroke in infancy, light-induced seizures, blastomycosis, intrauterine Caffey syndrome, vaccine-associated poliomyelitis in a child with agammaglobulinemia, and a comprehensive report with new observations of Robinow mesomelic dwarfism. He received the AAP Practitioner Research Award in 1988. In 1998, he published a book, *Pearls From a Pediatric Practice*.⁴³ His approach

is a model for practitioners with the interest and aptitude.

PRESERVE SPECIMENS

An excellent resource for detecting chemical toxicants that do not degrade with time are Guthrie dried blood spots originally used to test newborns for phenylketonuria. Hundreds of thousands of these blood samples are on file in hospitals throughout the United States, and abroad. They have been studied to screen >160 000 blood spots for 23 metabolic disorders in a single assay^{44,45} and to show that some cases of childhood acute myelogenous leukemia begin prenatally as indicated by a specific chromosomal abnormality.⁴⁶ (One child was 10 years old at diagnosis.) It was easy and inexpensive to collect the specimens, store, and retrieve them. The collection was population based, so bias is not an issue when random samples or entire collections are studied. This unplanned use is an extra dividend of immense value in research.

In Seveso, Italy, blood samples were stored in 1976 from people who had been in fallout from a cloud of dioxin created by a runaway reaction at a factory. Forty children developed chloracne. In 1991, after CDC scientists developed an assay for dioxin, the levels in blood taken 2 weeks after the exposure were up to 56 000 ppt in these children, as compared with ≤ 20 ppt in nonexposed people.^{47,48} The test was decisive in evaluating claims of illness from exposure of veterans who had been in ground forces in Vietnam.⁴⁹

In the spring of 2002, scientists at Washington University of St. Louis were making space in a remote storage facility when they happened on a collection of 85 000 infant teeth. A card gave information about each child. More than 2000, now middle-aged, were called and have agreed to fill in health questionnaires. The teeth were collected for the St. Louis Infant-tooth Survey, 1958–1970, for the purpose to which they are now being put; namely to link strontium levels in childhood to subsequent health events.⁵⁰

ROLE OF EPIDEMIOLOGY

Establishing Causality

A small number of unusual cases can, of course, be attributable to chance. To build evidence for a causal effect, a case-series or case-control study (epidemiology) will reveal details of the relationship. So it was in defining small head size and mental retardation among the children of the atomic bomb in Japan. A prospective (cohort) study of the children was part of the general health examinations performed biannually at the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki. It showed a dose-response effect for mental retardation and, beginning at lower doses, small head size, as described above.

Demonstrating a dose-response effect is important in establishing causality of suspected environmental hazards. In this instance, the same effect had been shown long ago in experimental animals, so its occurrence in the human was biologically plausible.

Among this cohort of <200 cases, there was no excess of leukemia or other cancers through 46 years of age.⁵¹ Outside Japan, studies of maternal diagnostic exposures of the abdomen late in pregnancy showed a 1.4-fold increase in almost every form of childhood cancer.⁵² One group of experts believes the excess is attributable to the exposure,⁵³ and another group says that it is not biologically plausible.⁵⁴ The effect has been sought in laboratory animals but not found. Also, the effect should be reproducible using other methods of study or other exposed groups. Cancer after in utero exposure to ionizing radiation has been found only in case-control studies, not in cohort studies.⁵⁴ Fourteen years earlier, in an editorial in the *New England Journal of Medicine*, MacMahon wrote, "It seems likely that the question of the association between fetal irradiation and childhood cancer will fade into medical history unresolved and remain a source of more confusion than enlightenment."⁵⁵

Disease Clusters

With regard to environmental causes of disease, epidemiology does best when applied to a substantial cluster of diseases, as in the first 350 cases of PCB poisoning in Kyushu, Japan; the outbreak of neurologic disease from methyl mercury-poisoned fish at Minamata Bay (also in Kyushu); and in the 5000 people in Tokyo subways who were poisoned in a terrorist attack in which sarin, an organophosphate pesticide, was released. Haruki Murakami, an award-winning novelist, has written a first-rate account based on interviews with victims, family members, and leading doctors.⁵⁶ The book is a major contribution to epidemiology and to preparing for terrorist attacks. (In Tokyo, physicians rose to the occasion. There was essentially no help from city authorities and city services.)

Epidemiology could not solve the puzzle of 16 infants with meningomyelocele in 6 months versus 4 expected in Atlanta, the home of the CDC,⁵⁷ or of 21 cases of childhood leukemia in Woburn, MA,^{58,59} or, as yet, of 16 cases of childhood leukemia in Fallon, NV.⁶⁰

Limits of Epidemiology

Epidemiology has not done well in detecting effects of environmental exposures that cannot be well defined. The problem has been described in *Science* by Taubes, whose article bore the title "Epidemiology Faces Its Limits."⁶¹ He made an epidemiologic study of epidemiologists by interviewing the best of them and found that almost all said that the increase in risk of a new finding had to be 3-fold or greater to merit attention. In a sidebar, risks this great were found in only 6 of 25 topics.

Childhood Cancer From Pesticides?

The International Agency for Research on Cancer publishes the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. The most recent reports show inadequate evidence for carcinogenicity in humans of dichlorobenzene, chlordane, heptachlor, and DDT.⁶² For children, exposed indoors and outdoors in many ways, the exposures have not caused the

TABLE 1. Main Childhood Cancers: Numbers of Studies, Statistical Comparisons, and Significant Excesses

Cancer	No. of Studies	No. of Statistical Comparisons	
		Total	No. With Excess
Leukemia	18	69	14
Brain tumors	18	106	21*
Neuroblastoma	7	7	0
Non-Hodgkin lymphoma	3	20	1
Wilms tumor	5	28	8
Ewing tumor	4	12	4
Other	13	26	7†
Total	68	268	55

Derived from Zahm and Ward.⁶³

* Twelve were from 1 study with 26 comparisons.

† Caldwell et al,⁶⁴ cluster of 10 colorectal cancer.

national rates for type-specific cancers to rise during childhood.

Epidemiologic studies of pesticides and childhood cancer have been reviewed exhaustively by Zahm and Ward.⁶³ The results, summarized in Table 1, are difficult to interpret. The children were exposed to a mixture of pesticides, and the childhood cancers have dissimilar carcinogenic mechanisms.⁵⁴ One study, different from the others, sought a cause for a cluster of 10 adolescents in Tennessee with colorectal cancer in a 26-month interval.⁶⁴ They lived in rural areas with high pesticide use. Serum levels of DDT, dieldrin, chlordane, and heptachlor did not differ from those of the control subjects. This is a model use of epidemiology—to study a cluster with objective measures of exposure.

Incidence rates are an important measure of changing environmental risks. Rising rates should take into account the influence of changing diagnostic criteria. An article on the front page of the *New York Times* on September 29, 1979,⁶⁵ reported an alarming rise in the incidence rates for childhood leukemia and brain cancer since 1973. In 1999, after careful analysis of the data by National Cancer Institute experts in demography, Linet et al⁶⁶ reported that “a modest rise in the incidence of leukemia . . . was largely due to an abrupt increase from 1983 to 1984; rates have decreased slightly since 1989.” They added that “the modest increases that were observed for brain/CNS cancers, leukemia and infant neuroblastoma were confined to the mid-1980s. The patterns suggest that the increases likely reflected diagnostic improvements or reporting changes.” For brain cancers, much improved radiologic imaging led to better diagnoses.⁶⁷

TABLE 2. Types of Childhood Leukemia Among Whites, Both Genders, Over Time*

Type of Leukemia	1973–1977			1978–1982			1983–1987		
	No.	%	Rate†	No.	%	Rate	No.	%	Rate
Acute lymphocytic	559	70		622	80		662	79	
Acute NOS	90	11		22	3		28	2	
Other leukemia	154	19		136	17		148	18	
All forms of leukemia	803	100	4.0	780	100	3.8	838	100	4.2

* Special tabulation from the Surveillance, Epidemiology, and End-Results Program of the National Cancer Institute, previously published by Miller.⁷⁰

† Per 100,000 per year, age-adjusted.

Example: A Sharp Rate Change Explained

A change in diagnostic criteria for acute lymphocytic leukemia (ALL), which accounts for 80% of childhood leukemia today, began in 1975, when Sen and Borella⁶⁸ described cell surface markers that differentiate ALL from other forms of leukemia. In the same year, Greaves et al⁶⁹ identified the common ALL antigen known as CALLA, which identifies B-cell lymphocytic leukemia (characterized by a tall age peak at 3–4 years). These advances led some leukemias of uncertain cell type to be reclassified as ALL. The percentages by cell-type changed abruptly, as shown in Table 2.⁷⁰

Eight percent of leukemia moved from “acute leukemia NOS [not otherwise specified]” in 1973–1977 to “acute lymphocytic leukemia” in 1978–1982. Selection of treatment depended on correct classification; ALL responded to treatment, but other forms of leukemia did not. Note that the total for all forms of leukemia in this time period showed only a minor fluctuation.

ENHANCING DISCOVERIES

1. When the AAP’s Practitioner Research Award was established, the hope was to publish a page in *Pediatrics* on the work that was honored. When that idea failed, the reports appeared in the *AAP News*. The announcements disappeared after a few years as a deluge of new section awards emerged, and only brief general descriptions were given for each, including the Practitioner Research Award. As a stimulant to research in practice, the *AAP News* could return to publishing descriptions of the specific work done.
2. As part of medical school or residency training, preparation of a case report would be valuable. (Cases that qualify for publication should add to what is already known or provide new insight into the disease and are not likely to be attributable to random occurrence.) A session on case reports could be held at AAP clinical meetings.
3. Identify future astute clinicians: medical students and residents who have the aptitude and interest as revealed by a special test, interviews, or performance. The aptitude may be indicated by creativity in curricular or extracurricular activities. Consider students who play with ideas, like late-night comedians.
4. Offer the opportunity to increase the aptitude through electives or postdoctoral positions with faculty members or National Institutes of Health scientists who are of a similar mind.

5. In obtaining the medical history, ask about hobbies, the occupation of the parents, and what they think might be the cause of the child's illness.
6. Fill blank spaces at the end of journal articles with short comments already written by peer reviewers, as in *Neurosurgery*. Interest in many clinical journals would be enhanced by adopting this practice.
7. In *Pediatrics*, consider putting articles about environmental hazards in a regular location in the Table of Contents. If placed at the end, for example, readers would grow accustomed to looking for them there. In the summer of 2002, the subjects so listed would have been June a) tattoos and body-piercing, b) sun-lamps tanning; July a) sun-burn, b) maternal bone-lead and fetal toxicity; August two on asthma.
8. Be open for serendipity. Look for information out of the ordinary of possible etiologic interest—in footnotes to tables or classified as “miscellaneous” or “other.”

Thousands of pediatricians routinely treated children who had feet that were scalded by tap water before Kenneth Feldman thought beyond treatment to prevention. He took action that was of national benefit. In the future, environmental hazards are likely to be recognized as in the past, by astute observers. Be prepared.

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