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NEUROLOGICAL CHANGES IN VINYL CHLORIDE-EXPOSED WORKERS

V. STŘEBLOVÁ[1], V. LAMBL[2], O. CHUMCAL[1], V. KELLEROVÁ[1], V. PAŠKOVÁ[1], J. VÍTOVCOVÁ[1], L. ŽLAB[1]

[1]) Department of Neurology, Medical Faculty of Hygiene, Charles University, Prague
[2]) Outpatient Clinic of Occupational Health, District Centre of National Health, Mělník, Czechoslovakia

Vinyl chloride (VC) toxicity for the human organism is not still fully clear. The occupational exposure to VC is linked with the development of liver hemangiosarcomas, or with other malignant processes of varying locality. Some authors diagnose changes in terms of scleroderma, universally are described roentgenologically detected lesions of interphalangeal joints and zonal osteolysis. They are described in association with Raynaud's syndrome (12, 10, 1, 4, 5 and others). Lange with his colleagues (12) describes angiologically detectable constriction of digital arteries, stenosis or partial occlusion of phalangeal blood vessels. Described are also various types of dysesthesia in fingers, particularly cold and numbness sensations. Also Byczkowska (3) reports frequent occurrence of finger paresthesia, whitening of fingers, but also of palms and soles, and other symptoms of peripheral vasomotor disorders.

Neurological manifestations are described only sporadically. Spirtas and colleagues (16) emphasize particularly the narcotic action of VC at higher peak exposure concentrations. This manifests itself by vertigo, nausea and headache pains. Mentioned are also hand paresthesiae (princkling, formication). Langauer-Lewowicka (11) analyzes also the clinical symptoms in her group of 200 examinees who showed most frequently signs of cerebellar symptomatology. She recorded frequent occurrence of headaches and sleep disorders, but also trigeminal neuralgia.

Because of a lack of more detailed neurological studies among the VC-exposed persons, we conducted field investigations among the occupationally exposed workers in a plant where there was six years before put into operation a workshop with a considerable VC hazard.

MATERIAL AND METHODS

The group of examinees consisted of 293 workers (263 males and 30 females), age 18—58 years, mean age 32.8 years. Of these 76 % were below 40. The average time of exposure was 2.8 years (range from 2 months to 6 years). After consultations with plant physician and plant toxicologist the group was divided into two subgroups according to the level of exposure. The subgroup of high-risk workers, in which the tentatively established maximum allowable concentration of 10 mg . m^{-3} had been frequently and sometimes highly exceeded, involved polymerization workers and some maintenance workers (a total of 109 persons). The subgroup of lower-risk category of workers included those engaged in drying and bagging operations, but even here they were sometimes exposed to high peak exposure concentrations during cleaning and sampling operations, and those from the other plant workshops — combustion, compressors, cracking, chlorination, regeneration — where the exposure risk was relatively low (a total of 184 persons).

All the workers were examined neurologically, some of them repeatedly. A more detailed analysis of subjective complaints was performed on the basis of EOD and N5 questionnaire surveys. Electroencephalographic examination with photostimulation was made in 232 persons (255 recordings). The group of controls consisted of 46 persons without exposure to toxic substances.

RESULTS

An overview of subjective complaints is presented in Table 1. Headaches occur frequently, but they are less frequent than in the control group. The incidence of gastrointestinal disorders and other neurovegetative disorders (palpitations, retrosternal pressure sensations) are significantly higher than in controls. Psychic disturbances were observed only in those exposed.

Table 1. Overview of subjective complaints in workers occupationally exposed to vinyl chloride, in a comparison with controls

Complaints	VC — exposed		Controls	
	number	%	number	%
Headache	46	15.7	9	19.6
Sleep disorders	16	5.5	2	4.4
GIT disorders	20	6.9	1	2.2
Vertigo	3	1.0	1	2.2
Psychic disturbation	13	4.5	0	0.0
Dysesthesia	9	3.1	1	2.2
Palpitations	14	4.8	0	0.0
Total number of examinees	293	100.0	46	100.0

Significant differences were observed between the two subgroups of exposed workers divided according to the level of exposure (Table 2). The subgroup of more exposed workers showed a higher incidence of headaches and

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Table 2. Overview of subjective complaints in workers occupationally exposed to vinyl chloride, relation to the level of exposure

Complaints	Total		More exposed		Less exposed	
	number	%	number	%	number	%
Headache	46	15.7	19	17.4	27	14.7
Sleep disorders	16	5.5	7	6.4	9	4.9
GIT disorders	20	6.9	11	10.1	9	4.9
Vertigo	3	1.0	2	1.8	1	0.5
Psychic disturbation	13	4.5	6	5.5	7	3.8
Dysesthesia	9	3.1	7	6.4	2	1.1
Palpitations	14	4.8	5	4.6	9	4.9
Total number of examinees	293	100.0	109	100.0	184	100.0

gastrointestinal disorders, and furthermore, of dysesthesia of extremities. There was observed also a certain correlation with the length of exposure (Table 3). In persons with the exposure time longer than 4 years, the incidence of headaches was double the incidence in the group with a shorter time of exposed for more than 4 years. Sleep disorders, gastrointestinal complaints, vertigo and psychic disturbances were also more frequent in those with a longer time of ex-

Table 3. Overview of subjective complaints in workers occupationally exposed to vinyl chloride, relation to the length of exposure

Complaints	Total		Exposure longer than 4 years		Exposure shorter than 4 years	
	number	%	number	%	number	%
Headache	46	15.7	24	23.8	22	11.0
Sleep disorders	16	5.5	8	7.9	8	4.2
GIT disorders	20	6.9	9	8.9	11	5.7
Vertigo	3	1.0	3	3.0	0	0.0
Psychic disturbation	13	4.5	8	7.9	5	2.6
Dysesthesia	9	3.1	8	7.9	1	0.5
Palpitations	14	4.8	4	4.0	10	5.2
Total number of examinees	293	100.0	101	100.0	192	100.0

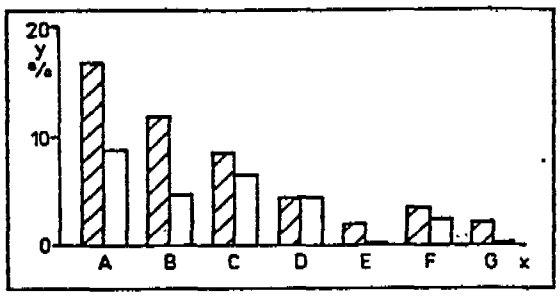
posed workers is characterized in Table 4. The group of more exposed workers showed a significantly lower per cent of normal findings and a higher per cent of more severe findings than the group of less exposed workers.

Graph 1 presents incidence of the most frequent, objectively diagnosed syndromes detected in exposed and control groups. The most frequent was the lesion of peripheral neurons, either motor or sensory, or both of them (16.8 % : : 8.7 %). Diagnosed were impairments of muscle tonus or trophicity, reduction or loss of tendon and bone reflexes, abnormal sensitivity. Compared to controls,

Table 4. Severity of objectively diagnosed changes in workers occupationally exposed to vinyl chloride in relation to the level of exposure

Severity of changes	Total		More exposed		Less exposed	
	number	%	number	%	number	%
Normal	165	57.0	50	46.0	115	62.5
Light changes	112	38.0	49	45.0	63	34.2
Manifest changes	16	5.0	10	9.0	6	3.3.
Total number of examinees	293	100.0	109	100.0	184	100.0

the group of exposed workers showed also more frequently the symptomatology of peripheral neurovegetative disorders (12 % : 4.4 %), specifically acrohypothermy, acrohyperhidrosis or whitening of fingers, associated with dysesthesia.



Graph 1: Objectively diagnosed changes in VC-exposed workers in a comparison to controls. X-axis — objectively diagnosed changes: A — peripheral neuron lesions, B — peripheral neurovegetative symptomatology, C — cerebellar symptomatology, D — vestibular symptomatology, F — extrapyramidal symptomatology, G — disperse central symptomatology. Blank column — group of controls, hatched column — group of VC-exposed. Y-axis — % of examinees

Graph 2 shows objectively diagnosed symptoms in relation to the level of exposure. A marked difference is in the incidence of peripheral neuron lesions: more exposed workers are affected more than twice as often (25.6 % : 11.8 %). Celebellar and vestibular syndrome is also more frequent (10 % : 7.6 % and 6.4 % : 3.3 %, respectively). There are also certain indications of a correlation with the length of exposure, see Graph 3: those with more than 4 years of exposure have more frequently peripheral neuron lesions (22.8 % : 13.6 %) and cerebellar impairments (13.9 % : 5.7 %). Frequency of the vestibulocerebellar syndrome is also higher (5 % : 0.5 %) in these persons.

The results of EEG examinations of exposed and 81 non-exposed control workers are compared in Table 5. The per cent of abnormal EEG recordings in the group of exposed workers is higher than in the control group; the EEG abnormities detected in the controls were always least severe. Abnormities

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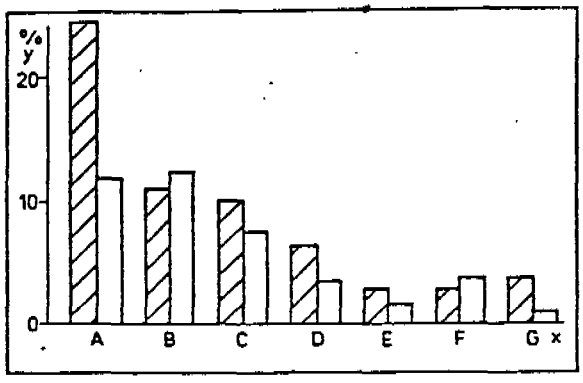
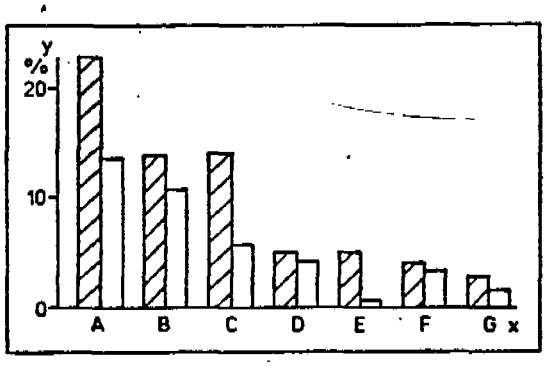
diagnosed in VC-exposed workers were predominantly episodic, in 5 cases combined with the diffuse abnormity. Three EEG recordings revealed only diffuse abnormities. Relatively frequent was also the presence of sleep waves (in 46.5 % of cases). In 16 % of workers the sleep activity manifestations were of



Graph 2: Objectively diagnosed changes in VC-exposed workers in relation to the level of exposure. X-axis abjectively diagnosed changes: A-D see Graph 1. Blank column — lower exposure levels, hatched column — higher exposure levels. Y-axis — % of the total number of exposed subjects.

a higher degree of severity (2c to 3, according to Roth (13)). Significant differences were observed also in the photostimulation reaction that was normal only in 40 % of cases. The most frequent was extension of photic driving towards beta and theta waves (in 43.4 % of cases).

The additionally conducted N5 and EOD (6, 7, 8, 9) questionnaire surveys were used to improve analysis of subjective complaints and to complement



Graph 3: Objectively diagnosed changes in VC-exposed workers in relation to the length of exposure. X-axis — objectively diagnosed changes: A-D see Graph 1. Blank column — exposure shorter than 4 years, hatched column — exposure longer than 4 years. Y-axis — % of the total number of exposed subjects.

anamnestic data. The questionnaire N5 examines superficial personal traits as well as certain clinical symptomatology, particularly neurovegetative syndrome, neurasthenic, depressive and anxiety-phobic symptoms, and the so-called toxic syndrome. Data provided by this type of questionnaire were suggestive of

Table 5. Severity of EEG changes in workers occupationally exposed to vinyl chloride, in a comparison to controls

EEG changes		Exposed		Controls	
		number	%	number	%
Normal		148	63.8	57	70.4
Suspect		48	20.7	19	23.4
Abnormal	slight	30	12.9	5	6.2
	medium	6	2.6	0	0.0
	total	36	15.5	5	6.2
Total		232	100.0	81	100.0

a higher frequency of sleep disorders (36 %) than originally revealed by anamnestic data, highly frequent (5 % level of significance) was also somnolence (76 %), which had not been also indicated in personal histories. More frequent were also feelings of bad performance, fear of loosing life or health. Furthermore, the frequency of hyperhidrosis was also very high (73 %). The Eyseneck personality questionnaire examines neuroticism. It reveals subjective tendencies that are evaluated by the examinee and confronted with the objective reality. In the examined group there were not detected any significant deviations from the norm; increased neuroticism could not be demonstrated.

DISCUSSION

Clinical examination of VC-exposed workers revealed significant changes predominantly in neurologic symptomatology. Some of the subjective complaints, such as headaches, vertigo, sleep disorders or increased sleepiness during the day, as revealed by questionnaire N5, are suggestive of the narcotic action of VC, similarly as the occurrence of the cerebellar and/or vestibulocerebellar symptomatology. These changes have been already described by Spirtas and colleagues (16), Langauer-Lewowicka (11), but also by Schwartzová (15) and others. This characteristic symptomatology was also described in our previous studies concerned with the occupational exposure to trichloroethylene, benzene and other organic solvents (17, 18, 20). Here we also observed a high incidence of dysesthesia after exposures to some solvents, particularly to benzene. We ascribed it either to peripheral vasomotor changes, or — at least in some cases — to initial phases of polyneuropathy. In case of VC the presence of peripheral vasomotor changes is evidently very significant: according to literature data

and to our own experience these changes are frequently associated with Raynaud's syndrome and may presumably lead to even more severe consequencies in terms of stenosis or occlusion, as described by Lange (12). Peripheral nerve lesions diagnosed in our group of VC-exposed examinees could be then explained by a direct neurotoxic action of VC, or as a consequence of hypoxia accompanying more severe vasomotor changes in the periphery.

The narcotic action of VC can be either transitory, inducing only reversible changes in the brain function, or persistent, causing more permanent, sometime irreversible changes in the CNS. Slight functional changes manifest themselves in EEG recordings by waves typical for various stages of sleep, as confirmed in a relatively high per cent (46.5 %) of cases in our group of examinees as well as in some of the examined subjects exposed to other organic solvents (19, 21, 22). Detection of episodic or diffuse EEG abnormalities is rather more serious and may be indicative of chronic changes in mediobasal and/or cortical brain structures. In our group of examinees, the joint episodic and diffuse abnormality occurred in 15.6 % of workers. This frequency is in agreement with the cited literature data as well as with our previous experience. This leads us to a conclusion that even VC, particularly at higher exposure concentrations, can produce neurotic changes in the above described brain structures.

VC-induced pathophysiological changes are believed by some authors to manifest themselves by the central neurovegetative dysregulation, as a result of changed hypothalamus functions (2). This localization, presumed by these authors on the basis of their experimental studies, seems to be in agreement with our findings of EEG episodic abnormalities.

We also believe that even FS reaction changes, recorded in our group of exposed workers, may be of importance in the early diagnosis of VC-induced damage. Comparable FS reaction changes were also described by Rousková (14) in persons exposed to other toxic agents.

CONCLUSIONS

1) Exposure to VC may lead, besides to other changes described in the literature, also to lesions of the nervous system. The onset and development of these neurologic changes depend on the VC exposure level and on the length of exposure.

2) Some of the neurologic manifestations are caused by the narcotic action of VC, such as certain subjective complaints and cerebellar and/or vestibulocerebellar syndrome. These symptoms can be transitory or persistent.

3) Among the important manifestations that are characteristic for VC action is, no doubt, the peripheral vasomotor symptomatology, sometimes in combination with the Raynaud's syndrome described in the literature. These vasomotor changes in the periphery may further develop, leading consequently to

more severe lesions of peripheral blood vessels. Equally important are the general neurovegetative manifestations (gastrointestinal and cardiovascular disorders, hyperhidrosis, etc.) that might result from the central neurovegetative dysregulation. Important are also symptoms of peripheral neuron lesions caused by a direct neurotoxic action of VC or by hypoxia-related mechanisms.

4) Episodic abnormality in EEG recordings seems to agree with the assumed involvement of hypothalamic structures (Basalajev and colleagues). It occurs even at exposure to the other types of organic solvents (15, 19, 21, 22) and may be indicative of a more diffuse affliction of mediobasal and cortical structures of the brain. Less severe manifestations of EEG sleep activity can be ascribed to the nacrotic action of VC, more pronounced sleep manifestations accompanied with abnormal EEG changes may be suggestive of more persistent changes in the CNS.

5) Neurological changes have not been so far sufficiently accentuated in the professional literature and, therefore, the monitoring of workers at risk is not conducted systematically and by suitable methods. It is necessary to ensure a neurological prevention in these occupationally exposed workers. Of the supplementary methods of examination there are recommendable, both for prevention and research purposes, to use EEG examination with photostimulation, questionnaires N5 and EOD, and electromyographic examination.

SUMMARY

Neurological examinations were conducted in 293 workers occupationally exposed to vinyl chloride. Subjective complaints were evaluated on the background of N5 and EOD questionnare survey analysis, EEG examinations, including photostimulation, were performed in 232 persons. The control group comprised 46 nonexposed subjects. Average time of exposure was 2.8 years, the longest time of exposure was 6 years.

Among the most frequent subjective complaints were headache, neurovegetative disorders and dysesthesiae, among objective findings dominated cerebellar and/or vestibulocerebellar syndrome, lesions of peripheral neurons and peripheral neurovegetative symptomatology. Subjective and objective symptoms were found to depend on the exposure level and the time of exposure.

EEG examinations confirmed in 15.5 % of cases abnormities, predominantly episodic, sometinmes combined with the diffuse abnormality. 46.5 % of the exposed showed presence of sleep activity as a consequence of VC narcotic action. The episodic EEG activity could be ascribed to lesions of mediobasal structures, or even to changes in brain cortex.

Our data have confirmed that vinyl cloride has a considerable impact on the human nervous system. Most frequent are lesions of vestibulocerebellar system and vigility disorders due to VC narcotic action. Frequent occurrence of peripheral symptomatology can be explained by a direct neurotoxic action of VC, or as a consequence of hypoxia caused by peripheral vasomotor changes.

As a rule, regular check-ups of VC-exposed workers do not include systematic neurological examinations. The systematic neurologic prevention, based on the assessment of clinical, EEG and/or EMG examinations, should become obligatory. Supplementary use of N5 and EOD questionnaire surveys is highly advisable.

RÉSUMÉ

Stýblová, V., Lambl, V., Chumchal, O., Kellerová, V., Paško-vá, V., Vítovcová, J., Žlab, L.: **L'image neurologique chez les sujets exposés au chlorure de vinyle**

Il a été étudié d'une manière complexe l'image neurologique chez 293 sujets exposés au chlorure de vinyle. Des troubles subjectifs ont été analysés au plan détaillé à l'aide des anquêtes EOD et N5. Il a été mis en évidence un effet neurotoxique significatif produit par chlorure de vinyle qui dépend de la qualité et de la quantité de l'exposition subie.

Les troubles subjectifs rencontrés le plus souvant: maux de tête, symptômes végétatifs et dysesthésie. Les données objectives témoignent pour une affection du système vestibulocérébelleux et pour celle du neurone périphérique et de l'innervation périphérique végétative. La symptômatologie périphérique peut résulter de l'effet toxique direct produit par chlorure de vinyle aussi bien que du mécanisme d'hypoxie ayant lieu lors des changements vasomoteurs périphériques.

Des donnés issues de l'EEG témoignant une activité de sommeil chez 46,5 % de sujets démontrent un effet narcotique du chlorure de vinyle. L'activité épisodique (chez 15,5 %) associée parfois à l'anomalie de diffusion pourrait s'expliquer par une atteinte des structures médiobasales, même liée aux changements du cortex.

Les sujets exposés à l'influence du chlorure de vinyle ne se soumettent, jusqu'à ce jour, aux examens systématiques au plan neurologique. Il est nécessaire de poursuivre, dans ce cas, une prophylaxie neurologique étudiant l'image clinique, les données issues de l'EEG ou même de l'EMG. Il est utile d'employer les anquêtes EOD et N5.

ZUSAMMENFASSUNG

Stýblová, V., Lambl, V., Chumchal, O., Kellerová, V., Paško-vá, V., Vítovcová, V., Žlab, L.: **Neurologisches Bild bei den dem Vinylchlorid exponierten Arbeitenden**

Man beobachtete kompiexerweise das neurologische Bild bei 293 Arbeitenden, die Vinylchlorid exponiert waren. Subjektive Schwierigkeiten analysierte man eingehender mit Hilfe der EOD- und N 5-Fragebogen. Dabei hat man eine signifikante neurotoxische Einwirkung von Vinylchlorid nachgewiesen, die von der Intensität und Dauer der Exposition abhängig ist.

Die häufigsten subjektiven Schwierigkeiten waren Kopfschmerzen vegetative Symptome und Dysesthäsie. Der objektive Befund zeugt von der Affektion des Vestibularzerebellarsystems, ferner von der Affektion des peripheren Neurons und der peripheren vegetativen Innervation. Die periphere Symptomatologie kann man erklären sowohl als direkte Einwirkung von Vinylchlorid, als auch den hypoxischen Mechanismus bei peripheren vasomotorischen Veränderungen.

In dem EEG-Befund stellte man bei 46,5 % Tiele der Gesamtheit die Schlafaktivität fest, die die narkotische Einwirkung von Vinylchlorid dokumentiert. Die episodische Aktivität (bei 15,5 %) manchmal in Verbindung mit Diffusionsabnormität könnte man durch Affektion von mediobasalen Strukturen, gegebenenfals durch Kortexveränderungen erklären.

Die Vinylchlorid exponierten Arbeitenden werden bisher systematisch vom neurologischen Standpunkt nicht beobachtet. Die Verfasser halten die gezielte neurologische

Vorbeugung in Verbindung mit Beobachtung des klinischen Bildes, des EEG- eventuell auch des EMG-Befundes für notwendig. Sehr geeignet ist die Anwendung der EOD- und N 5-Fragebogen.

RESUMEN

Stýblová, V., Lambl, V., Chumchal, O., Kellerová, V., Pašková, V., Vítovcová, V., Žlab, L.: El cuadro neurológico en trabajadores expuestos al viniicloruro

Se ha examinado globalmente el cuadro neurológico en 293 trabajadores expuestos al viniicloruro. Las dificultades subjetivos se las analizó detalladamente mediante los cuestionarios EOD y N 5. Se mostró el resultado neurotóxico marcado del viniicloruro, el que dependía de la altura y duración de la exposición. Las dificultades subjetivas más frecuentes eran los dolores de la cabeza, los síntomas vegetativos así que la disestesia. El hallazgo objetivo muestra la afectación del sistema vestibulocerebelar, así que la de la neurona vegetativa periférica y de a inervación vegetativa periférica. La sintomatología periférica la puede explicar tanto por el efecto tóxico directo del viniicloruro, como por el mecanismo hipóxico con los cambios vasomotóricos periféricos.

Se halló en hallazgos electroencefalográficos una actividad del sueño en el 46,5 p. c. del conjunto, lo que prueba el resultado narcótico del viniicloruro. La actividad epizódica (en el 15,5 p. c.), a veces en la combinación con la anormidad difusa podría se explicar por afectación de las estructuras mediobasales, eventualmente por cambios de la epidermis.

Los trabajadores expuestos al viniicloruro no son aún examinados neurológicamente de manera sistemática. Hace falta que se haya realizado neurológica prevención encaminada incluso el cuadro clínico, el hallazgo electroencefalográfico, eventualmente el electromiográfico. Se recomienda usar los cuestionarios EID y N 5.

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V. Stýblová, Dept. Neurology, Medical Faculty of Hygiene, Charles University, Šrobárova 50, 100 42 Praha 10, Czechoslovakia

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REVIEW ARTICLE

The origin of human cancers

John Cairns*

Imperial Cancer Research Fund, Burtonhole Lane, London NW7 1AD, UK

The limited evidence available suggests that most human cancers are not caused by conventional mutagens but are more likely to be the result of genetic transpositions. Although the molecular biology of transposition is starting to be understood, the external factors that influence its frequency have not yet been studied in any detail.

DIFFERENT human populations tend to suffer from different kinds of cancer: the inhabitants of third world countries have an excess of liver cancer, those of western nations have an excess of cancer of the breast and colon, the Japanese have an excess of stomach cancer, and so on. Most of this variation must be due to varied diets, customs and environment rather than to differences in genetic constitution, because nations have been observed to undergo changes in cancer incidence from one generation to the next and migrant populations tend to take on the pattern of cancer that is characteristic of their new homes. Cancer is therefore thought to be a preventable disease.

In the western world the two commonest cancers are cancer of the skin and the lung, and each of these happens to be so strongly dependent on a single factor (that is, sunlight and smoking) that their cause could be identified without the need for any understanding of the underlying mechanism of carcinogenesis. The preventable causes of the other common cancers are less clear-cut and it may be difficult to identify them until much more is known about mechanism. Eventually the techniques of nucleic acid chemistry should allow us to itemize all the differences in nucleotide sequence and gene expression that distinguish a cancer cell from its normal counterpart, and perhaps at that point the steps involved in carcinogenesis will cease to be in doubt. But until then we have to be content with circumstantial evidence. This review discusses the evidence and makes certain deductions about the molecular biology of human cancer.

Experimental carcinogenesis

Much of cancer research is based on the reasonable premise that we should be able to learn about human cancer by studying carcinogenesis in animals. During the 65 years since coal tar was shown to be carcinogenic for the skin of rabbits, many ways have been found for producing cancer in experimental animals. The problem is to decide which of these very diverse forms of carcinogenesis is likely to be the best model for most human cancers.

The easiest and most widely studied method is to expose the chosen target in the animal to physical or chemical agents that damage DNA. Because the carcinogenic potency of such agents is fairly well correlated with their ability to cause point mutations[1-3], these forms of cancer are commonly assumed to arise as the result of local changes in DNA sequence (in the rest of this article, the words 'mutation' and 'mutagen' are used specifically for such local changes). However, the process cannot be quite as simple as that. In most cases, repeated doses of the mutagen have to be administered over an appreciable fraction of the animal's lifespan, and in those few situations where a single dose of mutagen is carcinogenic the resulting cancer usually does not appear for a long time[4]. Thus the creation of a cancer cell is thought to involve a sequence of events of which perhaps only the early steps bear any direct relation to the interaction between mutagen and DNA. This is borne out by the observation that the later events can be caused by other agents ('promoters') that are not themselves mutagenic. The conventional explanation is that 'initiation' represents the production of mutants and that the subsequent steps of promotion are required because the relevant mutations either happen to be recessive (and so will only be detectable following deletion or somatic recombination) or usually involve repressor genes (and so are not expressed until the existing stock of repressor molecules has been depleted by further cell multiplication). But this type of interpretation is not without difficulties. The first step in the sequence seems to be too efficient[5-7]; in certain situations, even quite low doses of mutagen are capable of initiating the process in almost every exposed cell. Conversely, the later steps seem to be too sluggish[8,9]; in several instances, more than 10 cell divisions may be needed following initiation to achieve expression of the new phenotype in any of the descendent cells.

Cancers can arise following infection with certain viruses. Here the explanation seems at first sight more straightforward, for it is easy to see how novel phenotypes could result from an interaction between the genes of a virus and those of the host. However, the interval between initial infection by the virus and final appearance of the cancer can be a large fraction of the animal's lifespan[10], and so even here the exact biology of the carcinogenic process may sometimes be quite as obscure as in most chemical carcinogenesis.

Cancers can also be produced in animals by transplanting certain tissues, such as ovary[11] or embryo[12], into special sites where the cells can multiply without restraint; similarly, cancers may arise in the tissues next to implanted sheets of plastic, apparently because the cells have lost the restraining influence provided by contact with each other[13]. It seems unlikely that any conventional form of mutation can play a part in these types of carcinogenesis, particularly as the cancer cells produced by transplantation can sometimes be restored to a normal, regulated pattern f growth by transplantation back to more demanding sites[14-16].

Lastly, a number of cancers have been bserved to arise spontaneously in animals that are given unlimited food, but not

* Present address: Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115.

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in animals whose intake of calories has been slightly restricted[17]. The mechanism of carcinogenesis by these few extra calories is completely obscure.

Those seem to be the main ways of causing cancer in animals. It is not obvious what, if anything, they have in common, and in the absence of any additional source of information we could therefore have no way of knowing which of these experimental cancers are the best models of the common human cancers; and if we do not know that, we cannot guess what class of environmental agent is likely to be the most important factor in causing human cancer.

The genetics of susceptibility to cancer

When the precise chemistry of any biological process is in doubt, it has usually been helpful to determine what kinds of mutation affect the process. This stratagem has been applied successfully in working out various metabolic pathways and in identifying many of the components involved in the synthesis of macromolecules, and it would seem to be the surest way of finding out what classes of biochemical event tend to be rate-limiting for human carcinogenesis. The method is, however, subject to certain logical restraints.

(1) When the main effect of a mutation of a multicellular animal is to alter the phenotype of one particular class of cells, the fact that it also raises the incidence of cancer in these cells may not be relevant when we come to consider the cause of other cancers. For example, some forms of inherited immunodeficiency are associated with an increased incidence of certain rare cancers arising in cells of the immune system[18]; obviously, this tells us little or nothing about the origin of the common cancers in other tissues.

(2) In general, mutations that increase the incidence of any cancer should be interpreted with some caution. Going back to the previous example, it is conceivable that the leukaemias and lymphomas of immunodeficient children arise by some special pathway, so that they may not even be a good model for the leukaemias and lymphomas that occur in normal subjects.

(3) The most informative mutations are usually those that stop things from happening. For example, mutations that block the induction of aryl hydrocarbon hydroxylase make mice more sensitive to the short-term toxicity and less sensitive to the long-term carcinogenicity of certain polycyclic aromatic hydrocarbons[19,20]. If we could show that similar mutations in humans lowered the incidence of any of the common cancers, this would suggest that these compounds are important in human carcinogenesis. So far, however, such studies in human populations have been inconclusive[21,22].

(4) In practice, much of our information may have to come from negative evidence. For instance, if a mutation that completely blocked the metabolism of certain potential carcinogens had no effect on the incidence of cancer, this would constitute very strong evidence that these chemicals and their metabolic products were probably not important. In fact, the first case we shall consider is an example of negative evidence.

If the conventional dogma is correct and cancer is usually initiated by localized somatic mutations produced by the chemical mutagens in our environment, we would expect inherited defects in DNA repair to have a marked effect on the incidence of the common cancers. Yet this turns out not to be true. The test case is the disease called xeroderma pigmentosum (XP). This arises when both copies of any one of the genes involved in the main pathway for excision repair contain an inherited defect[23,24]. The result seems to be equivalent to the effect of the *uvr* mutations of *Escherichia coli* and *Salmonella typhimurium*, which make these bacteria into exquisitely sensitive tester strains for most chemical carcinogens. Like such bacteria, the cells of XP patients have a defect in DNA excision that makes them up to 10 times more sensitive to the lethal[25-32] and mutagenic[33-38] effects of most mutagens (the main exceptions being X rays and certain simple alkylating agents). As a result of this defect, XP patients are extremely sensitive to UV light. They suffer an age-specific incidence of skin cancer that is several thousand times higher than normal and they frequently die from malignant melanoma; as these skin cancers arise on the exposed parts of the body, they are presumably the result of mutations induced by UV light in the basal cells of the skin, perhaps coupled with some radiation damage to the local immune system of the skin[39]. Yet, even though the repair defect of XP patients extends to all the tissues that have been tested and apparently affects the response to all bulky lesions and major distortions of the double helix[24], it does not result in any obvious increase in the common fatal cancers (such as cancer of the lung, alimentary canal and breast). This is a striking anomaly, but it seems to have been pointed out only once before[40]. For example, not one death from internal cancer was recorded in any of the published clinical reports on series of XP patients[41-50] summarized in Table 1; and a survey of the entire literature on XP for the past 40 years[51] (which included a search through 6 years of US death certificates[52] and therefore must comprise many hundreds of cases) has revealed only seven internal neoplasms and only two or three deaths from cancers that could not have been caused by sunlight. Now, it is possible at this point to indulge in some special pleading—by arguing, for example, that XP patients do not live long enough to experience the common internal cancers which, for some as yet unknown reason, cannot be brought forward in time as readily as skin cancers. But the most reasonable conclusion is that the commonly fatal cancers are not caused by the kind of lesions of DNA that XP patients (and bacterial *uvr* mutants) are specifically unable to repair.

That conclusion is strengthened when we consider Bloom's syndrome, an inherited disease that apparently does increase the incidence of the common cancers. Its molecular biology is not understood, but the disease is associated with a high frequency of chromosomal aberrations and exchanges[53,54]. (Interestingly, the patients' cells do not show any very marked increase in sensitivity to various mutagens[24].) From a registry of cases it has been possible to calculate very crude estimates of 'life-tables' and of relative risk for carcinomas and for leukaemias and lymphomas (Fig. 1, Table 1). We see that the death rate from cancer is raised about 100-fold in each age group (Table 1). This demonstrates that it is possible to observe such increases in risk even when the number of subjects is small and their lifespan very limited; for XP, where the numbers are greater and lifespan is somewhat longer, it should have been even easier; in this sense, therefore, Bloom's syndrome serves as a control. (Two other inherited diseases, Fanconi's anaemia and ataxia telangiectasia, are associated with chromosomal instability, and they too show a high incidence of leukaemia; however, the published reports are not sufficiently detailed for the calculation of life tables.)

Comparison of the clinical records for XP and Bloom's syndrome therefore leads to the following conclusions. (1) For most people the main source of mutagenic lesions in DNA is UV light. (2) Chemical mutagens (of the kind detected in the usual tests for mutagenicity) seem unlikely to be the rate-limiting components in most human carcinogenesis. (3) Large-scale changes in the genome (such as rearrangements and deletions) seem to be more hazardous than the local changes produced by conventional mutagens.

The karyotype of human cancers

If genetic rearrangement or deletion is a critical step in the formation of most human cancers, the change might often be large enough to produce a visible alteration in chromosomal anatomy. Unfortunately, it is not easy to obtain good metaphase spreads for the cancer cells in solid tumours, and so most studies of karyotype have been confined to the leukaemias[55] and to a few solid tumours, such as meningiomas[56] and gliomas[57], which contain neoplastic cells that grow readily *in vitro*. In these

diseases, visible chromosomal rearrangements have proved to be more the rule than the exception, and for many cancers the karyotype has actually been observed to become progressively abnormal with time. It is therefore clear that at least the later stages in development of cancers are usually associated with large-scale changes in the genome.

For obvious reasons, much less is known about the earlier stages of carcinogenesis. About 90% of chronic myeloid leukaemias show a translocation from chromosome 22 to 9, which creates the characteristically shortened 22 known as the Philadelphia chromosome[58]; in several instances[59–61] the translocation has been observed to be present quite early in the sequence of events leading to the leukaemia, suggesting that it was primarily this alteration that allowed the precancerous stem cell to multiply without restraint and gradually colonize most of the bone marrow. (The exceptional cases of chronic myeloid leukaemia that do not have the translocation run a distinctly less favourable clinical course[62], and so they can probably be classified as a different kind of cancer, brought on by a different sequence of events.) Similarly, patients with ataxia telangiectasia are often found to be harbouring an expanding clone of lymphocytes with a translocation affecting chromosome 14 (refs 63, 64) and the lymphatic leukaemia which commonly occurs in these patients apparently develops within these clones. (Interestingly, myelomas and one class of lymphomas may also show translocations to chromosome 14 (ref. 65).) Those are the clearest examples where a particular change in karyotype appears to be an essential, early step in carcinogenesis. Of course, it is possible that still earlier in each of those sequences some crucial step occurred that made inevitable the subsequent emergence of cells bearing these particular rearrangements. For example, benign meningiomas have often been observed to be diploid in their early stages[66], and it is only later that they tend to be dominated by a characteristic cell that has lost one chromosome 22 (ref. 56); and there are certain kinds of cancer, such as acute myeloid leukaemia, that sometimes maintain an apparently normal karyotype throughout the whole course of the disease[66].

These studies of karyotype can therefore be interpreted in one of two ways. The obvious conclusion is that large chromosomal rearrangements are usually the crucial steps in carcinogenesis, but that there are exceptions and in certain classes of cell the critical changes either are not rearrangements or are on too small a scale to be detected by chromosomal banding techniques. It is, however, possible to argue that the cellular environment within any growing cancer is very abnormal and applies strong selection pressure for very unusual phenotypes, and these are most easily generated by large-scale rearrangements of the genome; the observed changes in karyotype could therefore be trivial secondary events that occur after all the rate-limiting steps of carcinogenesis have been completed.

The evolutionary analogy is worth pursuing a little further. The normal architecture and programmes of cell renewal in multicellular animals seem to be so arranged that the various multiplying stem cells do not, as a rule, compete with each other for territory[67]. For example, it is clear from studies of X-chromosome mosaicism that adult human tissues are made up of a large number of very small families of cells which therefore cannot be undergoing clonal selection[68,69]; similarly, the haematopoietic stem cells that circulate in the blood of mice are capable of establishing themselves in the marrow and forming clones of descendants, but they will only do so if the resident stem cells occupying the available sites in the marrow have been killed[70]. So one of the crucial steps in the development of a cancer must be the change that allows a stem cell to compete favourably with its neighbours and form an expanding clone within which further natural selection can then take place. We should therefore consider the possibility that the formation of a cancer proceeds by the same mechanism as the evolution of a new species. In other words, we might expect normal non-cancerous cells to be like species that are not evolving quickly: they will accumulate local alterations in base sequence and amino acid sequence due to forced or unforced errors in DNA replication, but these will tend to be neutral and have little effect on phenotype[71]. In contrast, a family of cancer cells should be like a species that is undergoing a rapid evolution in morphology. Such evolution is now thought to be due mainly to pleiotropic changes in the regulation of gene expression that are the result of large-scale alterations in gene arrangement and chromosome constitution[72,73]. In short, the analogy with evolution would predict that cancer should usually be due to gene rearrangements rather than to the local changes in sequence produced by conventional mutagens. Before considering what is known about the molecular biology of such rearrangements, it is worth examining the other half of the proposition, namely that carcinogenesis by conventional mutagenesis is not making a major contribution to the national incidence of cancer.

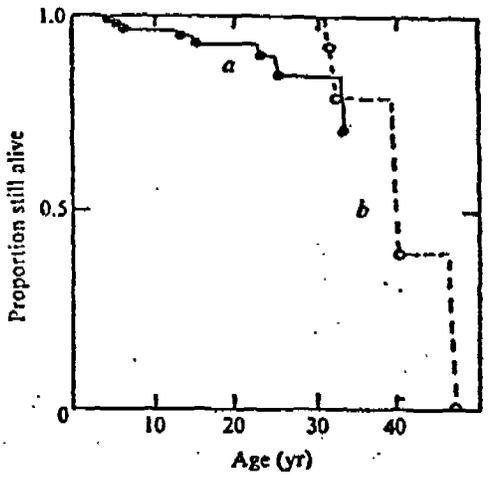

Fig. 1 Life tables for patients with Bloom's syndrome. The calculations have been based on a collection of 89 cases (J. German, unpublished), 12 of whom have died of cancer. *a*, Proportion who have not yet died of leukaemia or lymphoma; *b*, proportion who have not yet died of carcinoma.

Mutagenesis and cancer

It seems clearly established that localized lesions in DNA can be carcinogenic: for example, pyrimidine dimers must be the cause of the skin cancers produced when animals are irradiated with UV light, because the cancers can be prevented by photoreversal with visible light (a reaction that seems to be specific for dimers)[74]; similarly, the formation of O^6-alkylguanine in DNA is apparently the basis for carcinogenesis by certain alkylating agents because the cancers tend to be confined to the tissues that are unable to repair that particular lesion[75,76]. So the issue is not simply whether conventional mutagens are capable of causing cancer, but whether they reach our cells in sufficient quantity to make a major contribution to our present national incidence of cancer. In short, it is a question of the balance between dose of mutagens and the efficiency of our various pathways for DNA repair.

Although skin cancer due to UV light is the commonest cancer in western nations, it is seldom fatal and accounts for only 1% of all cancer deaths. But when there is a defect in the relevant DNA repair pathway (as in XP) the age-specific incidence of skin cancer can be raised several thousandfold and life-expectancy drop to about 20; this shows the extent to which an efficient system of repair is protecting us against one of the major hazards of our environment. Similarly, the repair pathway that handles the lesions produced by X-ray irradiation seems to be equally effective, because only about 1% of all cancer deaths are believed to be attributable to the natural sources of ionizing

radiation[77]. Presumably there has always been strong selection pressure for adequate methods of DNA repair, and so it is hardly surprising to find such low levels of risk from agents like UV light and X rays, which have not changed in intensity for millions of years.

There are reasons for thinking that our exposure to the chemical mutagens in our environment is now actually somewhat less than it used to be. The argument runs as follows[78]. Experimental animals tend to show a rather limited range of responses when mutagens are added to their diet; a few, very reactive chemicals produce cancer of the oesophagus and stomach, but most mutagens produce cancer of the liver. In humans, however, liver cancer accounts for only 1% of the cancer deaths in countries like the United States and Europe; oesophageal cancer is not very common outside certain parts of Africa, Iran and China; and stomach cancer is on the decline in all industrialized nations. So it seems likely that when affluence brings us the opportunity to choose what we eat, we tend to avoid foods heavily contaminated with mutagens and are therefore able to stay well within the capabilities of our DNA repair pathways. Actually, even in undeveloped countries the level of exposure to chemical carcinogens seems to be within most people's capacity for repair; in Africa, for example, the liver cancer caused by aflatoxin is largely confined to people chronically infected with hepatitis B virus[79], which indicates that although aflatoxin is known to be one of the most potent carcinogens for certain experimental animals it is not present in a high enough concentration even in Africa to produce many cancers in normal people.

So much for the 'natural' mutagens in our environment. Fortunately, the novel unnatural mutagens that we have met in the first half of this century as a result of our industrialization seem to be no more powerful than the natural ones[80]. Occupational cancers probably account for less than 5% of all cancer deaths[81]; and the number attributable to mutagenesis is actually less than this because a large proportion of today's occupational cancers are due to asbestos, which is negligibly mutagenic[82] although it is known to produce chromosomal abnormalities[83]. These numbers are, of course, trivial compared with the effect of tobacco. This has proved to be the outstanding carcinogen of the twentieth century and is now responsible for [illegible] cancer deaths. But it is not at all clear that these cancers can be classified as due to mutagenesis. Although cigarette smoke condensate contains mutagens[84], it is much more powerful as a promoter than an initiator in experimental carcinogenesis[85,86]. Furthermore, if tobacco were mainly acting as a mutagen, there should have been some reports of lung cancer in XP patients; after all, strong sunlight (which in normal people is about as carcinogenic as heavy smoking) can produce skin cancer in these patients by the time they are 7 years old, and so smoking should have given some of them lung cancer by the time they are 30.

All these arguments are indirect, but they do suggest rather strongly that local changes in DNA sequence, produced by conventional mutagens, are probably making only a minor contribution to our national death rates.

Table 1 Deaths from internal cancers

	Bloom's syndrome* obs./exp.†			Xeroderma pigmentosum‡ obs./exp.	
Age	Patient years	Leukaemias and lymphomas	Carcinomas	Patient years	All cancers (excl. skin)
0–4	340	1/0.013	0/0.017	640	0/0.059
5–14	640	3/0.020	0/0.019	886	0/0.055
15–24	327	2/0.011	0/0.016	450	0/0.036
25–34	108	2/0.005	2/0.013	213	0/0.035
35–44	16		1/0.008	109	0/0.038
45–54	3		1/0.005	54	0/0.107
Totals		12/0.127			0/0.330

The observed values were obtained from various clinical reports. For Bloom's syndrome the estimates are probably fairly reliable, because the condition is very rare and so the fate of each case is usually followed rather closely; of these 89 cases, 17 are known to have died (12 from cancer). Because XP is much less rare, cases tend to be reported but not followed up, and so the existing literature may be used to give some idea of their incidence of cancer but will give an underestimate of their death rate. During the limited period when these 140 cases were observed, 71 had had skin cancer (which was fatal in 8 cases), 1 had had a brain tumour and 1 had chronic myeloid leukaemia.

*89 cases (J. German, unpublished).

†Expected values were calculated from the current age-specific cancer death rates in England and Wales.

‡140 cases reported in refs 41–50.

Genetic transposition as a cause of cancer

In the last decade, the routes leading to genetic diversity have become much better understood[87,88]. Diffusion of heritable information is now known to occur not only by 'legitimate' recombination between homologous regions of different genomes, but also by 'illegitimate' recombination between largely nonhomologous regions (which can be in different parts of the genome or even in different individuals). The second of these processes is equivalent to a chromosomal rearrangement and allows the shuffling of certain modules of information ('transposons') so that new combinations of genes can be tested for survival advantage. The process depends on the presence of certain short sequences in the DNA that are the substrates for various recombinational enzymes ('transposases'), and it represents a much more drastic form of genetic variation than localized changes in base sequence because it can alter the expression of whole regions of the genome.

Transpositions can be site specific (for example, the changes in surface antigens of *Salmonella* and certain trypanosomes) or nonspecific (such as the spread of antibiotic resistance between different bacteria); they are usually solitary, but they can occur in clusters; and their frequency can vary from 1 per cell division down to 10^{-10}. A transposon can be the substrate for a transposase encoded elsewhere in the genome or it can make its own specific transposase. As the result of moving to a new site, a transposon can start or stop being transcribed; but the main effect can be not on itself so much as on neighbouring genes, which can be turned on or off or made unstable by its presence.

Transposition is therefore a very special form of genetic regulation because it can be programmed to occur at any predetermined rate, can be concerned with any desired number of alternative states, and can be made virtually irreversible. For example, the switch in the mating type of yeasts is the result of a transposition which occurs at a rate that is itself under separate genetic control[89]; but the change has all the characteristics of a step in differentiation because it concerns the function of a large number of genes but normally is confined to one particular branch of the cell lineage (the mother cells, rather than the buds)[90]. It is not yet clear whether transposition is important in vertebrate development. As the result of certain experiments on nuclear transplantation, there has been a tendency in recent years to regard the nuclei of the somatic cells of vertebrates as totipotential and therefore not fundamentally different from the germ line[91]. However, the fact remains that although it is easy to produce a normal animal using the nucleus taken from a fertilized egg or an early blastula cell, no one has ever succeeded in producing a normal animal using the nucleus taken from a somatic cell of an adult. It is therefore quite conceivable that changes in gene arrangement do occur during vertebrate development, especially as it is now known that antibody diversity is generated by specific transpositions that occur during differentiation of B lymphocytes[92,93].

As pointed out in the earlier sections of this review, there are good reasons for believing that the steps leading to human cancer are more likely to be transpositions than localized

changes in sequence. It is therefore important to find out what classes of external agents or features of cellular behaviour raise the frequency of such transpositions. Interestingly, conventional mutagens often appear to have no effect. Indeed, it was the inability of any mutagen to raise the spontaneous reversion rate of certain forward mutations in *E. coli* that initially marked out these mutations as being unusual[94] and eventually led to the discovery that they were due to the movement of insertion sequences; similarly, the movement of certain transposable elements in yeast has been found to occur 'spontaneously' but does not appear to be strongly catalysed by any of the common mutagens[95]. However, rates of transposition can be influenced by external factors. For example, transpositions are only a minor cause of mutation in rapidly multiplying bacteria[96], but they are a major source of forward mutations in stationary cultures[97]; the growth of *Drosophila* cells *in vitro* leads to the proliferation of certain repetitive sequences[98]; the frequency of the transpositions that produce variegation in *Drosophila* and in *Antirrhinum* petals is inversely related to temperature[99,100]; and the integration of a tumour virus can be associated with transpositions in the neighbouring host DNA[101]. Lastly, many mutagens are known to cause sister chromatid exchanges and other chromosomal interactions in mammalian cells, although it is not always clear to what extent these gross changes are functionally equivalent to genetic transpositions.

The assay of mutagens using bacterial tester strains has been one of the most fruitful practical results of molecular genetics. Its success stems from the fact that the chemistry of DNA is the same for all forms of life and so the chemistry of mutagenesis (and of repair) also tends to be the same. The molecular biology of transposition promises to be more idiosyncratic. The transposable genetic elements were discovered by McClintock[102] in 1950 and their possible role in carcinogenesis was first discussed by Temin[103] in 1970, but it is still too early for there to have been much systematic molecular biological investigation of the factors that trigger transpositions, either in prokaryotes or in eukaryotes. The rate of movement of most transposons will have been subject to evolutionary pressures and many transposons will therefore have acquired their own individual controls. Thus it may not be a simple matter to devise a general assay for the factors that drive the carcinogenic transpositions.

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BNA Current Report

Carcinogens

UNION CARBIDE FINDS NO CORRELATION BETWEEN CANCER CASES, PLANT EXPOSURES

Epidemiological studies by Union Carbide Corporation failed to find any correlation between brain cancer cases discovered at a Union Carbide petrochemical plant in Texas City, Texas, and employee exposures to chemicals used or manufactured at the facility, the company announced Nov. 11.

In a letter mailed to each employee at Texas City, Plant Manager Damon L. Engle and Plant Physician David H. Glenn said that the excessive occurrence of brain cancer "may represent a chance occurrence" and is not a result of any chemical exposure at the plant.

The Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health reported last year that they had found 18, and possibly as many as 25, brain cancer cases among employees at the Texas City plant. That was about twice the incidence rate found among the surrounding population, the agencies reported (Current Report, Oct. 30, 1980, p. 573).

Union Carbide's study, begun in 1979, found 12 deaths due to primary malignant brain cancer among the 6,588 Texas City employees studied. By comparison with U.S. rates, 7.42 cases would have been expected, the company stated.

The overall mortality rate of employees working at Texas City since 1941 is "significantly less" than the national average, 765 observed compared with 923.82 expected, according to the company.

Three reasons for labeling the four or five excess deaths a chance occurrence were given by Engle and Glenn:

- The company was unable to associate the deaths with any particular chemical exposures.
- The types of brain cancer found are present in the same percentages as those seen among the general population. Ordinarily, the company maintained, chemically caused cancer is a specific and often unusual type, different than those seen in the general population.
- Excessive brain cancer has not been confirmed in any chemical plant similar to the Carbide facility in any other part of the U.S.

"There is no cause for alarm," the company officials told the Texas City employees. They added that deaths due to cancer, "however small in number," will "continue to receive our attention and concern," and that Carbide will continue its investigations and cooperation with NIOSH in the agency's own on-going study.

Union Carbide said it expects that the NIOSH study will reflect conclusions similar to those of the Carbide investigation. Both studies used a common data base that includes the health and work histories of 6,588 workers who have been employed at the Texas City plant since 1941, according to the company.

Current standards and practices at the Texas City facility "provide more than adequate protection from known health hazards," Union Carbide asserted.

The Carbide study was reviewed by Dr. Brian McMahon of Harvard University and and Dr. Philip Enterline of the University of Pittsburgh.

NIOSH Responds

A spokeswoman for the National Institute for Occupational Safety and Health, while stressing that the institute was pleased with the cooperative professional relationship it has experienced with Union Carbide, nonetheless questioned some of the company's interpretations of the data.

Spokeswoman Deborah Van Brunt told BNA Nov. 16 that, although NIOSH could corroborate the overall results reported by the company, an additional finding was made of a threefold increased risk among employees who worked at the plant 20 years or longer. In addition, NIOSH said it was aware of 23 — not 12 — brain cancer cases, as reported in its preliminary findings in August 1980.

The institute also took issue with the three reasons stated by Carbide for speculating that the excess may have been due to chance.

First, the institute acknowledged that the the failure to find a correlation between particular exposures and the cases was "important evidence" but maintained that such evidence does not rule out an occupational hazard as the cause. Van Brunt added that the cause may be traceable instead to a class of chemicals or certain chemicals in combination with one another.

Second, the institute stated that brain cancer in general, as well as the types of brain cancer found at the plant, indeed represent an unusual and specific cause of death. Five such deaths usually are found among 100,000 w[illegible] males in the general population, the institute maintained, making it the sort of "unusual" cancer attributed to chemical exposures by Carbide. In addition, the institute questioned that company assumption, saying that common types of cancer are related to occupational exposures as often as are unusual types.

Third, the institute, while acknowledging that no similar excess had been confirmed at other locations, contended that unconfirmed higher-than-expected incidence rates found at several plants "raise a very strong suggestion of brain cancer as an occupational hazard." NIOSH gave as an example a Union Carbide plant at South Charleston, W.Va., which it said used similar chemicals to those at the Texas City facility. A twofold brain cancer excess was found there, it noted.

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