Occupational carcinogenesis

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Occupational carcinogenesis is one of the most interesting, tragic, important and difficult fields in oncology.

It is interesting from the scientific point of view because it represents, dramatically, an experiment in carcinogenesis made on humans and it may teach us a lot about the natural history of tumours. It is tragic from a human point of view, because work which is per se a natural necessity of life, should not, at least, cause cancer. It is socially important because oncogenic factors increasingly are produced and diffused in occupational environments. Moreover from the factories they spread to the general environment, so that they come to be an ecological problem. Finally, occupational carcinogenesis is a difficult field to approach, because the care of the workers' health is often in conflict with the productive interests of the factories.

Industry has done a lot for experimental carcinogenesis, related to occupational cancer; often however the result is merely to prove the carcinogenic effect in animals of agents which have already proved to be carcinogenic for man: this is equivalent to saying that many people die of cancer but some make their living from cancer. On the other hand emotional arguments should be avoided. Thus I am aware that speaking on occupational carcinogenesis is a complex and difficult task.

Experimental carcinogenesis did not start with the experiment of Yamagiwa and Ichikawa in 1915, but rather in the 16th century with the observation of the so-called 'mountain disease' in miners of Joachimisthal. This disease was recognized at the end of the last century as pulmonary carcinoma, which we now know is due to radio-active pollution, present in those mines. In 1775 Percival Pott in 'Chirurgical Observations' described a cancer of the scrotum in chimney sweepers and he correlated it with the black soot. In 1894 Unna reported on the frequency of skin cancer found in maritime workers, and he considered it due to excessive exposure to sun light. In 1895 Rehn, a surgeon from Frankfurt, reported at the congress of the German Society of Surgeons, 3 cases of bladder tumours found among 45 workers from a factory which produced fuchsine. He thought that the tumours were caused by aniline, but in fact it was shown, several decades later, that they were due to other aromatic amines. In 1902 at a meeting of the Medical Society of Hamburg, Frieben presented a case of a cutaneous tumour found on the hand of an employee of a factory producing X-ray apparatus. This employee used his hand for radiological demonstrations.

The frequency of reports on occupational cancer has been increasing with the increase of industrialization, mainly due to the progress of chemistry. The most important thing to do in occupational carcinogenesis is to try to recognize occupations which may represent an oncogenic risk, and to identify the agent or agents which cause the risk, and also to try to assess the degree of risk. If the risk is related to an agent already known to be oncogenic for man, its detection in the occupational environment should be considered sufficient for undertaking preventive measures. On the other hand if the risk is related to agents, whose effects on workers have not yet been studied and are therefore not yet known, then we have to evaluate the risk they represent for workers. This can be done by means of epidemiological investigations and experimental testing. Most oncogenic occupational agents have been identified on the basis of retrospective epidemiological studies.

The progress in and the development of this branch of oncology should facilitate systematic experimental testing of agents heavily released in the occupational environ-

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ment. In other words *epidemiological evidence in man should be avoided*. Experimental tests on animals are the more relevant to man, the more they reproduce the conditions of human exposure and eventually induce in animals the same tumours that they induce in man. In this case, the results of experimental tests may be considered largely equivalent to epidemiological evidence in man.

On the other hand if an agent causes any kind of tumour in animals, in whatever experimental conditions, it should be considered potentially carcinogenic for man. To consider an agent definitely carcinogenic for man on such a basis, would be an excess, but no time should be lost before retesting it in more appropriate conditions. To reproduce experimentally the conditions of occupational exposure is often difficult and costly. Furthermore we have to consider that the number of agents in the occupational environment is large and increasing.

Thus, new agents to which workers may be exposed should be submitted first to the easiest and quickest tests, however incomplete those tests may be. Then, for those agents inducing tumours in the experimental animals in these conditions, more precise and sophisticated experimental tests should be devised. The validity of experimental testing and the prerequisites for validity have been a matter of long discussions in international

TABLE 1 *Incidence of subcutaneous sarcomas in rats, following local injection of some inorganic pigments*

Treatment	No. of animals	No. of tumours
Chromium yellow (lead chromate)	40	26
Chromium orange (lead chromate)	40	26
Molybdenum orange (lead chromate and molybdenum chromate)	40	36
Cadmium yellow (cadmium sulphide)	40	15
Iron red (iron oxide)	40	1
Iron yellow (iron oxide)	40	0
Controls	60	0

FIG. 1 *Apparatus for inhalation of controlled doses of gaseous compounds, in the Experimental Unit of the Istituto di Oncologia di Bologna.*

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meetings and commissions, but of course, in the meantime the existing occupational exposure continues. Also, imperfect testing, for example the subcutaneous injection in the rat of compounds, to which man is exposed mainly by the respiratory route, may give some idea of their potential oncogenic risk.

In Table 1, data are reported on the induction of tumours (sarcomas) at the site of the subcutaneous injection of some inorganic pigments. From these data it clearly appears that chromium and cadmium pigments should be considered riskier than iron pigments. From what has been said before, the compounds shown to be carcinogenic in these conditions, should now be tested by inhalation. The latter way of exposure implies the availability of a complex apparatus for continuous inhalation of controlled doses. The apparatus is quite rare, as we discovered when we wanted to build one and we were not able to find any model in our own or any neighbouring country. Now an apparatus for inhalation of gaseous compounds has been functioning for more than two years in the experimental unit of our institute (Fig. 1).

With this apparatus we are now performing a carcinogenicity bioassay of vinyl chloride monomer (VC) and of vinyl acetate monomer (VA), which are (particularly the first) of great industrial importance. VC is used in the preparation of polyvinyl chloride resin, as a copolymer in saran and other plastics, as a solvent and as a chemical intermediate, and it is at present produced at a rate of 12,000,000 tons per year. Early results on these bioassays are shown in Table 2.

Zymbal glands carcinomas, liver angiosarcomas have never been observed as occurring spontaneously in our breed of Sprague-Dawley rats.

Only 3 cases of spontaneously occurring Zymbal glands carcinomas in rats (Sprague-Dawley) have been recorded in 1962. To our knowledge, no spontaneous nephroblastomas and liver angiosarcomas of rats have been reported in the literature. As far as we know, nephroblastomas have never been reported to be experimentally induced in rats; liver angiosarcomas have been induced in this species by diethylnitrosamine.

Although liver is the preferential site for onset of angiosarcomas, such kind of tumours have been observed in other tissues and organs: therefore VC should be considered in our experimental conditions generally cancerogenic for endothelia.

Zymbal glands tumours and nephroblastomas may be bilateral; liver angiosarcomas are often multiphocal.

Epidemiological investigations and medical controls should be undertaken on exposed workers. Would such neoplastic neoplasia unhappily be found in man, given the rarity of these tumours in both animals and humans, it would be a precise indication of the high value of experimental testing in predicting the oncogenic potential of environmental agents and would strengthen the recommendation on the necessity of such bioassays before any new industrial compound is produced and widespread in large scale.

Another means of revealing the oncogenic risk of an agent is to examine the exposed working populations with methods which make it possible to assess the incidence of cancer precursors. The incidence of such precursors has been studied by us by exfoliative cytology among asymptomatic, apparently healthy workers exposed to risk, namely among workers exposed to aromatic amines (urine cytology), and among workers exposed to chromates (sputum cytology). The incidence of cellular atypias in these two groups of workers is shown in Tables 3 and 4. It far exceeds the expected incidence.

To evaluate in medical and legal terms the risks represented by occupational oncogenic agents, we must consider that:

1. a direct relation exists between dose (amount and length of exposure) and neoplastic response;
2. the oncogenic agents produce mainly non-reversible changes, which may continue to develop when the exposure is interrupted;
3. the oncogenic agents (occupational or generally environmental) may be additive in their effects.

According to our knowledge the occupational carcinogenic agents may be classified as:

(a) definite carcinogens, when epidemiological evidence exists,

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TABLE 2 *Preliminary results of carcinogenicity bioassay of vinyl chloride monomer (VC) and of vinyl acetate (VA) (From C. Maltoni, G. Lefemine and L. Gualano, in press)*

Groups and treatment	Animals (Sprague-Dawley rats)		Animals with tumours					
			Zymbal glands carcinomas (A)	Nephroblastomas (B)	Angiosarcomas		Other type and/or site	Total
	Total	Survivors			Liver (C)	Other sites		
			No.	No.	No.	No.	No.	No.
I VA 2,500 ppm.	96	15	–	–	–	–	–	–
II VC 10,000 ppm.	69	–	13	3	6	–	5 (H)	27
III VC 6,000 ppm.	72	5	5	3	8	1 (D)	1 (I)	18
IV VC 2,500 ppm.	74	16	2	4	6	3 (E)	1 (L)	16
V VC 500 ppm.	67	15	2	3	5	2 (F)	1 (M)	13
VI VC 250 ppm.	67	20	–	3	1	2 (G)	2 (N)	8
VII VC 50 ppm.	64	35	–	–	–	–	–	–
VIII No treatment	68	33	–	–	–	–	–	–
Total	577	139	22	16	26	8	10	82

(A) Metastases to lung. (B) Metastases to liver and/or to lung and spleen. (C) Metastases to lung. (D) Angiosarcomas in subcutaneous fibrosing angioma. (E) 2 intrabdominal angiosarcomas (1 next to spleen and 1 next to ovary); 1 ossifying angiosarcoma of neck. (F) 1 pulmonary angiosarcoma; 1 angiosarcoma of uterus. (G) 1 intrabdominal angiosarcoma (next to spleen); 1 intrathoracic ossifying angiosarcoma. (H) 2 zymbal glands adenomas; 1 neurilemmioma of the ear; 1 mammary carcinoma; 1 cystoadenocarcinoma of ovary. (I) Sebaceous gland carcinoma of skin. (L) Zymbal glands adenoma. (M) Minimal deviation hepatoma. (N) 1 zymbal glands adenoma; 1 salivary glands carcinoma.

TABLE 3 *Frequency of cellular atypias among workers exposed to aromatic amines in 4 North Italian dye-stuff factories*

Cytological Atypias (Binucleation)

TABLE 3 *Frequency of cellular atypias among workers exposed to aromatic amines in 4 North Italian dye stuff factories*

Factory	No. of workers under control	Cytological classes (Papanicolaou)								
		I	I-II	II	II-III	III	III-IV	IV	IV-V	V
A	232	48	46	114	14	7	1	1	–	1
B	159	58	20	49	25	5	1	1	–	–
C	40	11	8	7	3	8	1	2	–	–
D	41	16	15	9	1	–	–	–	–	–
Total	472	133	89	179	43	20	3	4	–	1

TABLE 4 *Frequency of adenomatous typical and atypical hyperplasia, and of squamous metaplasia and dysplasia, in workers exposed to chromium compounds in one Northern Italian factory*

Type of occupation	Length of exposure (years)		Typical adenomatous hyperplasia		Atypical adenomatous hyperplasia		Squamous metaplasia		Squamous dysplasia	
	Length	No.	No.	%	No.	%	No.	%	No.	%
Production of chromates and dichromates	Up to 5	25	3	12	–	–	24	96	4	16
	6–10	14	3	21	1	7	12	86	3	21
	11–15	13	3	23	3	23	12	92	4	30
	Over 15	17	–	–	1	6	15	88	4	23
	Total	69	9	13	5	7	63	91	15	22
Production of chromium pigment	Up to 5	14	1	7	–	–	14	100	–	–
	6–10	17	1	6	–	–	14	82	2	12
	11–15	8	1	12	–	–	6	75	1	12
	Over 15	8	2	25	–	–	8	100	2	25
	Total	47	5	10	–	–	42	89	5	10

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(b) highly suspected carcinogens, when strong experimental and/or some epidemiological evidence is present,

(c) potential carcinogens, when experimental data give some indication of carcinogenic action of a compound on an experimental animal.

According to their effects, the carcinogenic agents may be classified as strong or medium.

The agents, which have been definitively proved or are suspected to be oncogenic for man on an epidemiological basis, are listed in Table 5, together with the target tissues and the degree of evidence. The list of the agents present in the occupational environment, which, on an experimental basis should be considered highly suspect or potentially carcinogenic for man, is reported in Table 6.

TABLE 5 *Agents proved or suspected to be oncogenic for workers on an epidemiological basis*

Agents	Evidence	Tumours
U.V. radiations	+	Skin carcinomas
X-rays	+	Skin carcinomas Leukaemias
Uranium ore	+	Pulmonary carcinomas
Arsenic	(+)	Skin carcinomas (lung carcinomas)
Asbestos	+	Lung carcinomas Pleural mesotheliomas (abdominal malignancies)
Chromium	+	Lung carcinomas
Nickel	+	Lung carcinomas Carcinomas of nasal and paranasal cavities
Iron ore	(+)	Lung carcinomas
Bis-chloromethyl ether	+	Lung carcinomas
Benzene	+	Leukaemias
Isopropylic oil	(+)	Carcinomas of paranasal cavities
Soot, tars, mineral oils, cutting oils	+	Skin carcinomas
Carbon black	-	Lung carcinomas
Mustard gas	+	Laryngeal carcinomas
Aromatic amines	+	Bladder and upper urinary tract carcinomas

TABLE 6 *Agents suspected to be carcinogenic for workers on an experimental basis*

Beryllium	Pesticides (DDT, aldrin, dieldrin, Aramite, DMDT,
Cadmium	Amizol, Thiuram)
Cobalt	Thiourea and related compounds
Lead	Tannins
Selenium	Detergents
Zinc	Alkylating agents
Carbon tetrachloride	Nitrosamines
Chloroform	Azo-dyes
Vinyl chloride	Oestrogens

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In Italy carcinogenic occupational risk exists for workers who are:

(a) exposed to chromates, mainly the ones working in factories where chromates are produced;

(b) exposed to nickel, mainly the ones exposed to nickel-carbonyl;

(c) exposed to asbestos, mainly the ones who extract it from its natural source, or workers in factories where asbestos is used for manufacturing;

(d) in factories making shoes, purses and raincoats, exposed to benzene;

(e) in factories producing carbon black from mineral oils; and

(f) in the dye and rubber industries, exposed to aromatic amines.

In our country occupational tumours have been observed in many of the above mentioned workers. 21 lung carcinomas have been found among less than 200 workers in a chromate factory in Northern Italy. Pleural mesotheliomas have been discovered among workers in asbestos mines. A number of leukaemias have been found among shoe-makers, who were heavily exposed to benzene, in factories in Lombardy (Vigevano), Bologna Province and Tuscany. The incidence of bladder and other urinary tract carcinomas among workers in 5 Italian dye-stuff factories are shown in Table 7. In these factories workers had been exposed to β-naphthylamine, benzidine, α-naphthylamine, Auramine, fuchsine, 3,3′-dichlorobenzidine. Now in our country the production of β-naphthylamine and benzidine has been withdrawn. One may conclude that prevention of occupational carcinogenesis is a very urgent problem.

The methods of prevention may be summarized as follows:

1. correct experimental testing of all newly used agents;
2. up to date epidemiological data from various categories of workers exposed to risk;
3. legislative measures forbidding the production and the utilization of agents which have been shown to be oncogenic on an epidemiological and/or an experimental basis, especially if the said agents are strong carcinogens;
4. measures of technical protection, when weak or doubtful carcinogens continue to be produced or employed; these protective measures should be periodically examined by Public Health Inspectors;
5. specific medical checks to make possible, on the one hand, the early detection of preneoplastic lesions and tumours, and on the other, the quantitative evaluation of the risks through the incidence of these changes.

It is my opinion that the value of medical checks is mainly to evaluate the risk that is epidemiological. Early detection of occupational tumours which, as already shown, are mainly located in the respiratory and urinary tract, has been, I think, over-emphasized. We know that these tumours are multicentric. In other words all the target apparatus is in some way affected by the carcinogenic process.

TABLE 7 *Frequency of carcinomas of the urinary tract among workers of 5 Italian dye-stuff factories exposed to aromatic amines*

Factory	Total No. of exposed workers	No. of workers with carcinoma		
		Bladder	Renal pelves and ureters	Total
A	286	17	1	18
B	586	87	5	92*
C	213	44	–	44
D	135	4	–	4
E	135	7	1	8
Total	1,155	159	7	166

* In 1 case bladder and upper urinary tract tumours were coexistent.

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Concerning the urinary tract, in a systematic histological study, I have seen that in patients with bladder tumours, dysplastic and cancerous foci may be detected from renal pelvis to urethra. Therefore it is obvious that in such conditions early diagnosis can achieve very little. We may diagnose some tumours quite early, but on the basis of 15 years' experience with periodic checks of workers exposed to high risk, I doubt that periodical medical examination has a real bearing in saving people with occupational cancer although detected early, or in prolonging their life span. Thus my position is in sharp contrast with those who claim to 'protect' (!) workers exposed to carcinogenic risk with medical examinations. *I do believe that the potentialities of medical examinations should be evaluated at an international level.*

In conclusion, I would like to emphasize the need of a close collaboration among scientists, public health services, workers unions and industries, to evaluate the risks and to devise preventive measures for avoiding or minimizing occupational tumours.

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