Cancer Incidence in the Population of Nagasaki City 30 Years after Atomic Bombing

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OKUYAMA, S. and MISHINA, H. *Cancer Incidence in the Population of Nagasaki City 30 Years after Atomic Bombing*. Tohoku J. exp. Med., 1988, **155** (1), 23-39 — In order to attest the evolutionary hypothesis of non-epithelial-epithelial tumor shift (Okuyama and Mishina 1986), the published cancer incidence data for the population of Nagasaki City during the period of 1973-1977 was studied along with appropriate control populations of Fukuoka City, and Miyagi and Osaka prefectures. Significant increments of non-epithelial tumors including leukemias, and epithelial tumors such as cervical cancers and choriocarcinomas were observed. An inference was made to the post-atomic bomb radiation carcinogenesis that different organ systems responded to that irradiation with different oncogenic patterns: Neoplasms of the pre-vertebral organs (non-epithelial organ systems) were the first to react and tapered long (curve type I); Tumors of the vertebral but pre-mammalian (those of the digestive tract, respiratory and thyroid) could have formed two separate peaks, one for the early and high dosage and the other for the late and low dosage (II); With breast cancer or the mammalian symbol tumor, there was a single peak reflecting the cohort of reproductives (III). The evolutionary and phylogenetic progression could have taken place from I through III. Thus, cancer incidence analysis may be helpful in deciphering the atomic bomb radiation carcinogenesis. ——— atomic bombing; evolutionary concepts of cancer; late cancer incidence; radiation carcinogenesis

When we examined the epidemiological aspects of cancer based on the published WHO data (Waterhous et al. 1982), there seemed to be a predominance of non-epithelial tumors during the period of infancy to adolescence, and that of epithelial ones thereafter (non-epithelial-epithelial tumor shift) (Okuyama and Mishina 1986). In the hope of obtaining an insight into the underlying evolutionary mechanisms, the epidemiological studies were expanded to include the population of Nagasaki City 30 years after the atomic bombing. In spite of probable dilution of the fraction of the atomic bomb survivors, the investigation was thought valid enough because the radiation is penetrating, and because carcinogenetic manifestation of radiation would take quite a long time. The results were thought to imply that the atomic bombing may possibly still have a hold on that victim population.

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MATERIALS and METHODS

Cancer incidence data for the 5-year period of 1973-1977 published in a WHO publication (Waterhous et al. 1982) were used throughout. There were 4 Japanese populations cited therein: 2 cities of Fukuoka and Nagasaki, and 2 prefectures of Miyagi and Osaka. The population size of each was as follows: in Fukuoka, 2,056,064 males and 2,210,330 females; in Miyagi, 960,245 males and 995,022 females; in Nagasaki, 214,005 males and 236,189 females; and in Osaka, 4,132,495 males and 4,146,430 females. A separate report tells that the population of Nagasaki City contained atomic bomb survivors to 37.8% in toto (33,037 or 33.4% of males and 48,964 or 41.6% of females, all of whom aged 25 years or above) (Ikeda et al. 1986). No data were available for Hiroshima yet.

Epidemiological studies on cancer based on an evolutionary concept have appeared to be more elucidating than those of the conventional presentation (Segi et al. 1981; Okuyama and Mishina 1985b, c, 1986, 1987). The human organ systems can be categorized into epithelial, non-epithelial and gonadal (evolutionarily secured). The non-epithelial group contains the hematopoietic system, brain, kidney, bone and other connective tissues while the epithelial is to include the gastrointestinal system as well as the hepatobiliary, respiratory organs and thyroid, and the breast, uterus and prostate, the mammalian symbol organs. The gonads are designated as "evolutionarily secured" because the gonadal cells have to be protected or easily be eliminated for the sake of conservation of the species when damaged, and in principle DNA repair that is prone to err is not permitted. Classification of mammalian vs. pre-mammalian was also employed. The latter was again divided into the homeothermic and poikilothermic (Okuyama and Mishina 1985c). The homeothermic organs are those that could have fully evolved in order to take advantage of the increased atmospheric oxygen concentrations during the carboniferous period and therefore are related to energy expenditure. The respiratory system and thyroid gland (Kobayashi 1975) may be included here.

Statistic analysis was carried out according to the method described elsewhere (Ipsen and Feigl 1970).

RESULTS

Cancer incidence in Japan 30 years after the atomic bombing

The published data on cancer incidence rates which had already be corrected for the standardized populations and annually averaged (ASR) were used as well as crude average annual incidence (Table 1). Although the crude incidence varied rather widely among the populations, the ASR world for the control populations of Fukuoka, Miyagi and Osaka appeared consistent, and fell on the

TABLE 1. *Crude average annual cancer incidence in Japan (1973-1977) and ASR world (age standardized rates)*

		Nagasaki	Fukuoka	Miyagi	Osaka
Males	Average	0.28%	0.08%	0.206%	0.16%
	ASR*	301.9	201.9	208.9	204.9
Females	Average	0.24%	0.07%	0.154%	0.138%
	ASR*	216.1	143.9	139.0	137.9

*ASR per 100,000 population.

TABLE 2. Age evolution of the age-standardized cancer incidence at 30 years post-atomic bombing (1973-1977)

Age groups	Nagasaki vs. Miyagi			
	Males		Females	
	Nagasaki	Miyagi	Nagasaki	Miyagi
0-14	79.0	28.0	49.3	23.9
15-24	42.4	21.9	35.7	24.3
25-34	86.1	50.0	142.1*	79.5
35-79	9791.3	6967.2	7460.7†	4045.9

*Includes in situ cancer of the cervix uteri (the total uterine cancer ASR were 14.6 for Nagasaki and 5.6 for Miyagi, respectively).

†The same were 704.8 for Nagasaki and 333.7 for Miyagi, respectively.

Fig. 1. Age-distribution of cancer incidence in the population of Nagasaki City 30 years post-atomic bombing as compared with the data from Miyagi Prefecture during the period 1973-1977. The average annual age-standardized rates (ASR) were plotted against the age: higher ASR were noted with the Nagasaki data in both the non-epithelial tumors (neoplasms of the hematopoietic, brain, kidney, bone and connective tissue) and epithelial. The contribution of the gonadal tumors to the trends did not appear great enough. A, Males; B, Females. It seemed curious enough that the high incidence was a universal phenomenon nearly all through the ages from the newborns to the elderly. Grave radiation effects or something else?

range of 202 and 209 in the males while that for Nagasaki was as high as 309. With the females, these values were much lower, but the trends appeared identical.

Age evolution of the age-standardized cancer incidence 30 years after the atomic bombing

On Table 2 shown are the significantly higher cancer incidence rates of people of Nagasaki City 30 years following the atomic bombing than the control populations. The difference was apparent roughly all through the ages in both sexes (Fig. 1). There were no discrimination among the non-epithelial or epithelial in terms of higher cancer incidence with the Nagasaki population. When their relative incidence was calculated and compared, the incidence of the non-epithelial tumors was higher with Nagasakiese than Miyagiese (Fig. 2). The non-epithelial-epithelial tumor shift, however, took place as it did in the control population. In the females, to the contrary, it took place 10 years earlier. The leukemic incidence was much higher all through the ages in both sexes (Fig. 3).

Fig. 2. Age spread of the relative cancer incidence in the population of Nagasaki City 30 years following the atomic bomb radiation. A, Males. The phenomenon of the non-epithelial-epithelial tumor shift was seen to take place in the Nagasaki population as expected. However, a definitely higher incidence of the non-epithelial tumors was to be seen from the infants through the elderly. No acceleration was apparent in spite of the exposure of fractions of the Nagasaki population to the atomic radiation. B, Females. An acceleration was seen to the rising limb of the epithelial tumors in the females.

Fig. 3. Age spread of leukemia incidence in the population of Nagasaki City 30 years following the atomic bomb radiation. When compared with the data from Miyagi males, the leukemogenic effects of the atomic bombing can be surmised population-wise, too, as amplified through processes of aging or accumulation of disintegrations of DNA so as to ultimately hit the *i* and *t* protooncogenes. Curiously again, the higher levels were observable throughout the ages. A, Males; B, Females.

The increments appeared greater with advancing ages in the males after middle age while they paralleled in the females. Lymphosarcomas and multiple myelomas seemed to be responsible for the higher incidence in the male.

TABLE 3. Age-standardized cancer incidence among the mammalian vs. pre-mammalian symbol organs (1973-1977)

			Nagasaki	Fukuoka	Miyagi	Osaka
Mammalian symbol	Prostate breast & uterus	Males	9.3	9.1	4.6	2.3
		Females	60.8*	43.6*	37.9	32.4
Pre-mammalian						
Homeo- thermic	Thyroid & respirat. organs	Males	43.4	30.8	29.9	27.8
		Females	17.2	11.0	10.6	10.2
Poikilo- thermic	Digestive organs	Males	156.3	123.7	133.6	93.2
		Females	100.2	79.3	83.8	59.6

*Includes in situ cervical cancer.

TABLE 4. *High cancer incidence in the population of Nagasaki City 30 years after the atomic bombing (1973-1977) : Statistical analysis on individual mammalian symbol organs*

High incidence of	Significance of Nagasaki City against :			
	Miyagi Prefecture		Osaka Prefecture	
	Male	Female	Male	Female
Nonepithelial	Yes*	Yes*	Yes*	Yes*
Breast cancer		No		No
Cervical cancer		Yes*†		No
Ovarian cancer		No		No
Choriocarcinoma		No		Yes*

*Statistically significant at $p < 0.01$.

†Includes carcinoma in situ, however, in the Nagasaki data.

Relative cancer incidence along the line of evolution of animal life

In spite of its merits in the elucidation of cultural influence (Okuyama and Mishina 1988), when cancer incidence in terms of ASR Japan was compared

Fig. 4. Age spread of gonadal tumors in the population of Nagasaki City 30 years following the atomic bombing. A, Testicular tumors. The tumor incidence in Nagasaki was not high at all. B, Ovary tumors. In the population of Nagasaki City, the incidence appeared higher at 50 years of age and thereafter, presumably representing the carcinogenetic effects of the atomic bomb radiation on the gonads.

Fig. 5. Age spread of cancer incidence of the mammalian symbol organs. A, Uterine cervical cancer. As was the case with the controls, there were 2 peaks of higher incidence in Nagasaki, one during the period of active reproduction, and the other postreproductiveness. The incidence in Nagasaki was significantly higher than in Miyagi control ($p < 0.01$). Undisputable contribution to the heights from inclusion of in situ cancers seemed probable. The transitional values from other controls may be suggestive of contribution of other factors such as viral etiologies, too. Thus, the radiation did not appear to affect the incidence pattern of cervical cancer. B, Uterine choriocarcinoma. The incidence curves were bi-peaked as in the controls. The peaks were definitely higher than any of them ($p < 0.01$). However, they apparently shifted leftward, suggesting possible accumulation of DNA damage in that population.

among the different organ groups of definite evolutionary implications, that is, the mammalian symbol organs, homeothermic and poikilothermic, the cancer distribution among them was identical between the populations of Nagasaki and other controls, although their ASR values were significantly greater in Nagasaki (Table 3). When the rates were compared of the individual female mammalian symbol organs, noteworthy discriminations seemed to turn out. There were significant rises in the uterine cervical cancers and choriocarcinomas, although definite conclusions have to be reserved for cervical cancers on account of the inclusion of carcinomas in situ (Table 4). Higher incidence were observed in both reproductive and postmenopausal periods with cervical cancers, not differing from the control populations (Fig. 4). With choriocarcinomas, however, there were two higher peaks with Nagasaki, and they both appeared earlier than the control peaks, too (Fig. 5).

DISCUSSION

This was not a direct survey among the atomic bomb survivors. The original victim population of Nagasaki City has been diluted of its residual radiation morbidity by the incoming and outgoing of the people of the city during the past 30 years as well as deaths of the survivors from other etiologies as time passed and as the city grew larger. It should also be noted that persistent low dose radiation could have been possible from the contaminated air, water and soils even among those who had not been in the city at the time of that radioactive explosion. Nonetheless, we thought that this type of survey was indispensable in order to see if and how the whole body exposure to atomic bomb radiation or fallouts or activation radiation would affect the cancer incidence in terms of the evolutionary concepts of cancer. Topical irradiation did not appear sufficient enough in this regard. Unfortunately, we could not locate any integral statistics of cancer incidence of Nagasaki or Hiroshima yet (Shigematsu and Kagan 1986).

In spite of the possible limitations of epidemiological survey (Travis 1975), the present analysis of cancer morbidity data of Nagasaki even 30 years after the bombing seems to have clarified the following: (1) The age evolution of neoplasms was significantly higher than the control; (2) The higher incidence of the non-epithelial tumors was due to the increments in lymphosarcomas and multiple myelomas; (3) Of the mammalian symbol organs, the incidence of uterine cervical cancers was higher; (4) Of the evolutionarily secured, there was a higher incidence of choriocarcinomas, although there can be one or two disputes in its epidemiological significance (Bracken et al. 1984); (5) In the female, the non-epithelial-epithelial tumor shift took place 10 years earlier in the population of Nagasaki City than in that of Miyagi Prefecture. Are they really related to the atomic bomb radiation in one way or another? What can be their implications in terms of the evolutionary concepts of cancer?

The human cancer incidence, as described elsewhere (Okuyama and Mishina 1988), seems to show the following dynamic and evolutionary characteristics: (i) A phenomenon of non-epithelial-epithelial tumor shift with advancing aging; (ii) Cancers of the mammalian symbol organs and those of the homeothermic evolution are more prevalent among the USA citizens than among the Japanese in Japan while the vice versa is true of those of the poikilothermic life; (iii) Cancers of the breast and uterus, the female mammalian symbolism, are prevalent in two distinct age regions, one, active reproductiveness and the other, post-reproductiveness, and with prostatic cancers, however, post-reproductive only; and (iv) With those of the pre-mammalian organs, the incidence curves are of exponential growth, mostly starting to rise beyond 30 years of age.

The present investigation was primarily intended to make it clear if and how the radiation per se affects the processes of carcinogenesis. The atomic bombing in Hiroshima and Nagasaki could have well served for that purpose if wholesome

Fig. 6. Neoplastic development in the population of Nagasaki City following the atomic bombing. The curves were composed based on the data of Ichimaru et al. for leukemia (1986), Kato (1986) and Monzen and Wakabayashi (1986) for epithelial tumors. The non-epithelial-epithelial tumor shift seems to have taken place in the case of chronological evolution of radiation carcinogenesis. Cancers of the mammalian symbol organs looked as if they had represented a cohort migration of the reproductive until they submerged into the contamination from those of the postreproductiveness.

publications were available. According to the descriptions, (a) cancer incidence is definitely higher in the population of Nagasaki City than the 3 control Japanese populations; (b) The increments were roughly dose-dependent; (c) However, what was noteworthy was that both the relative and absolute risks of oncogenesis of the survivors were “paradoxically” greater among the 0-9 rad groups than the 100+ rad; (d) Taking into account the fact that there were then no definite curative regimens for most of the epithelial cancers, the time of death could just be translated into the approximate time of diagnosis. Then, the data from comparison of age at death can be understood to denote that the shortest latency for clinical emergence of neoplasms was determined by the age of the survivors at the time of exposure rather than the radiation dosage, that is, the older the age at exposure, the shorter the latency (Kato 1986); (e) Taking into account the data of excess incidence/ 10^6 PYR for selected neoplasms (Kato 1986; Monzen and Wakabayashi 1986) and leukemia incidence data on the survivors (Ichimaru et al. 1986), a hypothetical “incidence function” scheme can be drawn as shown in Fig. 6. The above-mentioned paradoxical dose response would probably be resolved if we can take into account the time factors. The critical data for the first surges of cancer incidence are permanently lost, presumably because of difficult data collection under the circumstances. The data of our analysis may, therefore, be representing the latter portions of the function curves.

The leukemia rates among the non-exposed Nagasakiese are reported to have risen after 1958 while those of the survivors exposed in the vicinity of hypocenter attained the peak during the period 1950-1951 as surveyed during the period 1945-1965 (Itoga 1967). This finding may possibly be consistent with the present

Fig. 7. Evolutionary stratification of the anti-cancer mechanisms. As evolution progressed, there could have been several biological necessities eventually leading to acquisition of a host of defense mechanisms which were, however, not necessarily intended to defend against carcinogenesis. Nonetheless, the resultant effects were to include those of anti-cancer. By and large, the most primitive neoplasms could have been leukemias of DNA disintegration. The second category of neoplasms could have been cancers of disintegrative etiology with multiple disintegrations. Lymphomas could be younger, resulting from potent and continued antigenic stimulation and reactive lymphoproliferation. The most novel neoplasms may be lymphomas as the result of retroviral infections in the sense that the oncogenic information is derived from the humans or primates, and therefore, of the most recent origin.

population-wise data 30 years later. The problem can be how the carcinogenetic effects of the atomic radiation could have spread throughout that population as will be discussed below.

DNA damage, whether as the result of potency of the oncogene products (immortalizing factors (*i*) (Hanafusa et al. 1977)) and/or sensitivity of the rapidly renewing systems, would certainly lead the way to oncogenesis among the non-epithelial organs. For example, single activation of *c-myc* is probable with leukemias and neuroblastomas. Such seems to be the case with leukemias of Fanconi's anemia in which both deficiency of Cu, Zn-SOD (Yoshimitsu et al. 1984) and defective DNA repair (Ahmed and Setlow 1978) would cooperatively increase the probability of oncogenic activation and/or formation of novel oncogenic DNA changes (Leukemias of disintegrative type (Fig. 7)). For oncogenesis of the epithelial systems, transforming factors (*t*) have to be generated along with the immortalizing capacity (Hanafusa et al. 1977; Land et al. 1983; Ruley 1983), and there can be other barriers for such "cancer babies" to eventually emerge clinically (cancer phanerosis).

Coming back to the atomic radiation oncogenesis scheme, the curves I and II could have resulted as (*i*) or (*i* + *t*) took place with the high dose exposure groups. The first peaks of the II group must have receded by the year 1959 in order for the above-mentioned paradox to be adequately explained. Their second peaks are to result from (*i* + *t*) and aging. The curve for breast cancer (III) did not have the

TABLE 5. *Evolutionary fitting of atomic bomb radiation carcinogenesis :
A hypothetical model*

Evolutionary age	Symbol organs	Fitting curves
Evolutionarily secured	Testis and ovary	III (Ovary)
Vertebral		
Mammalian symbols	Prostate, breast and	III
Premammalian	uterus	
Homeothermic	Thyroid and	II
	respiratory	
Poikilothermic	Digestive tract	II
	Brain, kidney and bone	(I)
Pre-vertebral	Hematopoietic	I

first portion presumably because of the absence of sensitivity of the breast towards the carcinogenetic stimuli prior to puberty and after menopause. As soon as the candidate fraction of the population arrived at puberty and reproductiveness, the curve started rising. It may look like a cohort labeling of erythrocytes with radioiron in which labeled cells submerge from the bone marrow, circulate in the peripheral blood, and then eventually disappear from senescence. By the same token, we may predict that prostatic cancer would also present a cohort of increased incidence. Those data for the ovarian tumors revealed a curve III (Tokuoka 1986), although no data were available for the testicular tumors. A higher incidence in cases of chronic lymphocytic leukemia, chronic myeloid leukemia, lymphosarcoma and multiple myeloma is known toward the end of the curve I. This has to be the case with those fractions of people with lower doses of radiation exposure, and synergism with aging cannot be excluded, although they may be the minority. We do suspect that these curves may possess some evolutionary significance as will be discussed soon.

We have already presented an idea of classifying the organ systems into several categories along the long time axis of evolution as described in the section Materials and Methods (Okuyama and Mishina 1984, 1985a, b). Table 5 shows how snugly the curves fit the evolutionary categorization of organ systems. Radiation carcinogenesis following the atomic bombing thus seems to reiterate phylogenetic sequence of different organ systems as expected. This type of knowledge may facilitate our understanding of the matter, and hopefully developing novel diagnostic and therapeutic measures as well (Okuyama and Mishina 1985b, c; Okuyama et al. 1987).

Choriocarcinoma may constitute a distinct neoplastic category because it is a graft-versus-host reaction of the fetal, mostly male, against its mother cells. Radiation damage on the DNA in general is repairable. In the testis, however,

those damaged testicular cells may not always be repaired and they have to be eliminated by the special process of apoptosis (Harrison 1975). The DNA lesions produced in the spermatids may not be repaired. However, an abrogation of such lesions, if fertilization takes place, can be attained either by repairing with the repairing enzymes of the ovum or by abortion by the time of implantation (Prasad 1974). Choriocarcinoma is essentially a disease resulting from the oncogenic gene expression (Sarkar et al. 1986) on the part of the fetus, and therefore, an analysis of incidence of the disease could possibly have offered one of the most sensitive indicators of radiation effects from the atomic bombing. The *c-myc* and *c-ras* both were activated and expressed, and therefore, a two-step carcinogenesis of $(i + t)$ was probable. As reported earlier (Ujeno 1985), choriocarcinoma is probable even with very low radiation, and its oncogenesis is one of the repair defective, "disintegrative" types (Sheppard et al. 1985) as in the case of Fanconi's anemia (Okuyama and Mishina 1987). This tumor may constitute one of those of the evolutionarily secured organs. The entire picture how it had resulted from the atomic radiation remains obscure, and we cannot categorize its curves. However, it may be feasible to make a conjecture as follows: On the part of males: (i) Age range of reproductiveness at the time of exposure; (ii) Radiation dosage (With higher doses, permanent sterility ensues; with lower doses, transient sterility because of apoptosis of the spermatids as well as glandular atrophy. (iii) When they recover, the DNA damage is probable. If it should remain unrepaired at the time of fertilization, a host of abnormalities are probable (Sheppard et al. 1985). On the female part: (iv) Age range of reproductiveness can be the sole limiting factor so long as the incidence curves are concerned. Thus, (v) the morbidity would not accumulate beyond certain limits, and the curves would taper thereafter. (vi) Contribution of the background radiation may not always be determinable. The testicular absorbed doses in Nagasaki at the time of explosion is estimated to be 6870 rad at 500 m, 852 rad at 1000 m, 109 at 1500 m, and 13 rad at 2000 m from the hypocenter (Hashizume et al. 1974). The residual radioactivity at the hypocenter 60 days later was as 0.3 mR per hr, and it was 0.03 at most within 1000 m. Therefore, the estimated exposure for a man entering the hypocenter one hr after the explosion and standing there for infinity could have been expected to be 1.4 R at best. The fission product fallout occurred predominantly in Nishiyama district of Nagasaki 3 km east of the hypocenter (Pace and Smith 1946). The residual radioactivity 60 days later was 1.0 mR per hr at most. Then, the similar estimate of exposure could have been 10 R at most (Arakawa 1968). Nonetheless, there could have been measurable radioactive emanation as the result of thermal neutron activation of the rocks and soils: for example, 122 keV gamma rays from Eu-152 whose half life is as long as 13 years (Maruyama 1986). The background radioactivity of Nagasaki area, however, seems to have sufficiently decayed by the time the nation-wide radioactivity survey was carried out during the period of 1968-1977: it was 8.8 ± 0.8 micro R

per hr which was absolutely within the national average range (7.4–10.6) (Abe et al. 1969). Then, cancer candidates may not only be limited to the direct atomic bomb survivors and those who had entered the city, but also those who lived in the city for sometime after the detonation as the result of exposure from the high background radiation and possibly those whose parent or parents were exposed to radiation in one way or another as described above (Itoga 1967). Thus, there seems to be sufficient circumstantial evidence to believe that chromosomal aberrations that are to result in untoward oncogene expression and induce choriocarcinomas (Sugimori et al. 1978; Sarkar et al. 1986). Then, a surmised curve for choriocarcinoma may possibly look like that for breast cancer (III).

Apparently, the atomic radiation carcinogenesis by and large seems to have thus followed the sequence of oncogenesis through the evolutionary stratification as suggested for Fanconi's anemia (Fig. 7) (Okuyama and Mishina 1987). It may not have generated any novel carcinogenetic mechanisms, but have accelerated and sustained the natural leukemogenesis. It did not produce any novel bizarre types of leukemias so long as the reports were concerned. The sequence of events,

Fig. 8. Neoplastic evolution: a hypothesis based on the earthly history of DNA damage and its repair (Asada 1976; Ahmed and Setlow 1978), evolution of the immune systems (Kumagai 1985), epidemiology of lymphomas (Schwartz 1986), neoplastic evolution in AIDS (Kaplan et al. 1987), and discussion on the evolutionary significance of Fanconi's anemia (Okuyama and Mishina 1987). Leukemias resulting from unrepaired DNA damage or disintegrative type of tumor development could have been the most archaic forms of tumors because the single immortalization seems not infrequently sufficient enough in inducing leukemias, and an additional transformational events are needed in solid tumors (Hanafusa et al. 1977). The retroviral infection-neoplastic conversion may be the most novel forms of tumors because the evolution of the retroviruses is again the most novel.

however, seems to well agree with the law of biochemical evolution of Horowitz (1945): the evolution of the basic syntheses proceeded in a stepwise manner, involving one mutation at a time, but the order of attainment of individual steps has been in the reverse direction from that in which the synthesis proceeds in the chain, and the ultimate synthesis was the first to be acquired in the course of evolution, the penultimate step next, and so on. If we can take it for granted that the most essential component of carcinogenesis is the DNA change, then we may suppose that the type of carcinogenesis resulting from disintegration of that genetic material could have been the very initial process. Then, by and large the most primitive neoplasms in terms of biology could have been leukemias of DNA disintegration: The acquisition of DNA repair by means of excision can be as old as 2800 million years ago (Kondo 1978). And defective DNA repair and other chromosome breakage syndromes give rise to leukemias (Schwartz 1986; Okuyama and Mishina 1987). The second category of neoplasms could have been solid epithelial tumors of disintegrative type with multiple disintegrations. The NK cell could have been developed in order to cope with such neoplasms (Kumagai 1985). The cellular and humoral immunity could be traced back some 400 million years (Good et al. 1965). These structures, however, could have contributed to lymphomatogenesis as the result of potent and continued antigenic stimulation and reactive lymphoproliferation. The most novel neoplasms may be lymphomas resulting from retroviral infections in the sense that the oncogenic information is derived from the human or primates, and therefore, or the most recent origin (Gallo et al. 1977; Matthews 1983; Kaplan et al. 1987). Not to say, there has to be a multitude of pro and con carcinogenesis-related mechanisms that have been evolved and stratified in the carcinogenesis other neoplasms in between (Fig. 8). Thus, application of Horowitz' law to the science of carcinogenesis may possibly bear out important enough.

Population-wise radiation exposure may be a constant menace world-wise as was clearly seen in the power plant accident of Chernobyl, USSR, in 1986. We shall be able to attest our evolutionary concepts of cancer as the data will come out in the future so as to supplement the earliest portions of the Nagasaki curves. Nevertheless, we shall be able to predict the probable carcinogenetic aftermaths for that accident, too.

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