Fanconi's Anemia as a Nature's Evolutionary Experiment on Carcinogenesis

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— In order to obtain insights into the possible carcinogenetic mechanisms, the cancer incidence of Fanconi's anemia (FA) was surveyed in the literature, and the results were compared with those of other cancer-prone diseases of chromosomal breakage, and primary and secondary immunodeficiency syndromes along with an appropriate control population. With FA, there were 43% of leukemias but no lymphomatous diseases. Epithelial tumors consisting of hepatomas and squamous cell carcinomas were 17 and 38%, respectively. Their age distribution was 14.5 ± 6.7 years of age for leukemias; 18.5 ± 9.3 for hepatomas and 23.8 ± 6.9 for squamous cell carcinomas. Putting aside the hepatomas which may be iatrogenic, the neoplastic trend here again is to show the non-epithelial — epithelial tumor shift (Okuyama and Mishina 1986). Fanconi's anemia can thus be one of the chromosomal breakage syndromes whose leukemogenic and carcinogenetic processes are amplified by an increased DNA damage, NK cell depletion, and IgA deficiency as the result of deficient Cu, Zn-SOD and increased superoxide toxicity.
——— carcinogenesis; epidemiology; evolutionary concepts of cancer; Fanconi's anemia

There appear to be two major groups of diseases in which the patients are greatly prone to develop malignancies: One in which repair of the DNA damage is impaired (Xeroderma pigmentosum, Fanconi's anemia and Bloom's syndrome), and the other in which immunologic competency is drastically deviated (Schwartz 1986). In terms of the carcinogenetic mechanisms, Fanconi's anemia is of special interest, for there are two cardinal molecular defects in that syndrome. One is the reduction of cellular superoxide dismutase (SOD) activity (Yoshimitsu et al. 1984; Scarpa et al. 1985), and the other the defective repair of DNA damage (Ahmed and Setlow 1978). In the general populations, childhood malignancies are characterized by the predominance of non-epithelial tumors such as leukemias and tumors in the brain, kidney and bone, whereas that of the adult consists 90% of epithelial tumors, that is, the phenomenon of non-epithelial — epithelial tumor shift (Okuyama and Mishina 1986). That kind of chromosomal abnormality such

as trisomy 21 that has been established by the time of birth, to the contrary, exclusively helps emergence of leukemias (Rosner and Lee 1972).

With most of the immunological incompetence, the resulting tumors are mainly leukemias and lymphomas (Kersey et al. 1974). Tumors arising in Bloom's syndrome are intriguing enough because the non-epithelial ones are to predominate during the early periods of life but are replaced by cancers in the adulthood (German et al. 1977). In Fanconi's anemia, however, cases of cancers also are reported in spite of the chromosomal breakage as reviewed (Dosik et al. 1970; Reed et al. 1983). Thus, there have to be more extensive epidemiological studies on that topic and adequate comparison with other Nature's carcinogenetic experiments as well in order to obtain further insights of the matter. The results to be reported here seemed to suggest that the Nature would sometimes betray herself by defecting the archaic anti-cancer defense lines of circumvention of superoxide toxicity, DNA repair and immune surveillance of distinct evolutionary significance.

MATERIALS and METHODS

Evolutionary categorization of organ systems. Epidemiological studies on cancer based on an evolutionary concept have appeared to be more elucidating than those of the conventional presentation (Okuyama and Mishina 1986). The human organ systems can be categorized into epithelial, non-epithelial and gonadal (evolutionarily secured). The non-epithelial group contains the hematopoietic system, bone, kidney, brain and other connective tissues while the epithelial is to include the gastrointestinal system as well as the hepatobiliary, respiratory organ and thyroid, and the breast, uterus and prostate, the mammalian symbol organs.

Collection of cancer cases. This was carried out by searching in the literature cases of Fanconi's anemia accompanied by neoplasms. There were 86 of such. They were classified in accordance with their tumor categorization: Leukemias, lymphomas, brain, kidney and bone (non-epithelial) and cancers (epithelial). The data for the control population were obtained for males, Miyagi Prefecture, Japan, covering the 5-year period of 1973-1977 as reported in a WHO publication (Waterhouse et al. 1982).

RESULTS

On Table 1 listed are the 85 cases of Fanconi's anemia accompanied by neoplastic development as reported in the literature during the period of 1952-1987. Their spread along the axis of evolution was 45% non-epithelial and 55% epithelial (Table 2). Among the non-epithelial tumors, 43% were leukemic and 1% brain tumors. Their age distribution analysis revealed the average age of developing leukemias was 14.8 ± 6.5 (s.d.) years (37), and among the epithelial tumors, it was 18.5 ± 9.3 (17) for hepatomas, and 23.9 ± 6.8 (33) for squamous cell carcinomas (Fig. 1). In most cases, submission to hepatomas was related to prolonged administration of oxymetholone for the sake of treatment of pancytopenia, especially anemia.

TABLE 1. *Malignancies in patients with Fanconi's anemia*

Case No.	Author	Year	Age	Sex	Type of malignancy
<i>Non-epithelial neoplasms</i>					
<i>Leukemias</i>					
101	Auerbach et al.	1982	6	F	AML
102	Berard	1975	19	F	AMoL
103	Berger et al.	(1980-81)	15	M	EL
104			14	F	EL
105			18	F	EL
106	Bourgeois and Hill	1977	6	M	AMMoL
107	Cowdell et al.	1955	27	M	AML
108	Dosik et al.	1970	4	M	AMoL
109	Gastearna et al.	1982	9	M	EL
110	Goetz et al.	1974	9	F	AL
111	Lévy et al.	1974	10	F	AMoL
112	Meddeb et al.	1986	16	F	AMoL
113			10	M	ALL
114			19	M	EL
115	Meisner et al.	1978	15	F	EL
116	Obeid et al.	1980	10	M	ANLL
117	Prindull et al.	1979	15	M	EL
118	Rotzak et al.	1982	22	M	EL
119	Sarna et al.	1975	21	M	AL + hepatoma
120	Schaison et al.	1983	20	M	AL
121			8.5	F	AL
122			8.5	F	AML
123			10	M	AML
124			7	F	AML
125			11	F	AML
126			5	M	AML
127			13	M	EL
128			6	M	AML
129	Schroeder et al.	1979	29	F	AMMoL
130	Silver et al.	1952	13	F	AML
131	Stein et al.	1981	23	M	AMMoL
132	Stivirins et al.	1984	25	F	ANLL
133			18	F	ANLL
134	Submoke and Kessacorn	1985	—	—	AML
135	Taher et al.	1981	14.5	M	EL
136	Tanzer et al.	1980	25	M	AMoL
137			15	M	AMoL
138			23	M	AMoL
139	Zawartka et al.	1976	11	M	AML

TABLE 1. *Continued*

Case No.	Author	Year	Age	Sex	Type of malignancy
<i>Brain, Kidney and Bone</i>					
201	de Chadarevian et al.	1985	1.5	F	Medulloblastoma + Wilms' tumor
<i>Epithelial neoplasms</i>					
<i>Adenocarcinomas of the liver and stomach</i>					
301	Abbondanzo et al.	1986	11	F	Hepatoma
302	Bernstein et al.	1971	20	M	Hepatoma
303	Cap et al.	1983	10	M	Hepatoma
304	Cattan et al.	1974	22	F	Hepatoma
305	Guy and Auslander	1973	38	M	Hepatoma + tongue cancer
306	Hill et al.	1981	21	M	Stomach cancer
307	Holder et al.	1975	11	M	Hepatoma
308	Johnson et al.	1972	27	M	Hepatoma
309			21	M	Hepatoma
310	Kew et al.	1976	34	F	Hepatoma
311	Mokrohisky et al.	1977	6.5	F	Hepatoma
312	Sarna et al.	1975	21	M	Hepatoma
313	Schmidt et al.	1984	14	F	Hepatoma + AL
314			8	M	Hepatoma
315	Shapiro et al.	1977	13	M	Hepatoma
<i>Squamous cell carcinomas of the skin and/or oroesophagus</i>					
401	Abels and Reed	1973	22	M	Cancer, skin
402	Abo et al.	1980	22	F	Cancer, esophagus
403	Esparza and Thompson	1966	26	F	Cancer, esophagus
404	Guy and Auslander	1973	38	M	Cancer, tongue
405	Kaplan et al.	1985	13	F	Cancer, tongue
406	Kennedy and Hart	1982	22	F	Cancer, tongue
407	Kozarek and Sanowski	1981	26	M	Cancer, esophagus
408	Kozhevnikov and Khodorenko	1986	14	M	Cancer, oral mucosa
409	McDonough	1970	20	F	Cancer, gingiva
410	Nara et al.	1980	23	M	Cancer, gingiva
411			14	F	Cancer, gingiva
412	Reed et al.	1983	25	M	Cancer, pyriform sinus
413	Röckelein et al.	1986	32	F	Cancer, esophagus
414	Romero and Ortiz	1984	20	F	Cancer, esophagus
415	Sarna et al.	1975	21	M	Cancer, gingiva
416	Schofield and Worth	1980	30	F	Cancer, tongue
417	Swift et al.	1971	23	F	Cancer, gingiva

TABLE 1. *Continued*

Case No.	Author	Year	Age	Sex	Type of malignancy
418	Swift	1981	38	F	Cancer, tongue
419	Vaitiekaitis and Grau	1980	8	F	Cancer, gingiva
<i>Squamous cell carcinomas of the female genitalia</i>					
501	Arnold et al.	1980	28	F	Cancer, cervix and vulva
502	Hersey et al.	1982	22	F	Cancer, cervix
503	Kennedy and Hart	1982	21	F	Cancer, labium majus
504	King and Arnold	1980	28	F	Cancer, vulva
505			—	F	Cancer, vulva
506			—	F	Cancer, vulva
507	Ortonne et al.	1981	24	F	Cancer, vulva
508	Swift and Hirschhorn	1966	31	F	Cancer, vulva
509	Swift et al.	1971	31	F	Cancer, vulva
510	Wilkinson et al.	1984	22	F	Cancer, vagina
511			22	F	Cancer, labium

AL, acute leukemia; AML, acute myeloid leukemia; AMoL, acute monocytic leukemia; AMMoL, acute myelomonocytic leukemia; EL, erythroleukemia.

DISCUSSION

What are the Nature's experiments here? Cancer is a disease syndrome resulting from untoward expression of the protooncogenes or derangement and subsequent expression of any de novo gene abnormalities (Cronkite 1974; Klein and Klein 1984). The Nature provided the life on earth with the repairing abilities such as excision repair of DNA damage as early as 2.8 billion years ago (Kondo 1978). The major defense mechanism of Cu, Zn-SOD is thought to have been acquired 420 million years back (Asada 1976). The T cell evolution is surmised dated back 500 million years, and the emergence of the B cell and constitution of lymph nodes as late as 350 and 150 million years ago, respectively (Good et al. 1965). These biological acquisitions must have closely related to the physicochemical alterations on the earth: Reduction of intensity of the ultraviolet rays reaching the earth as the atmospheric oxygen concentrations started rising (excision repair); Maximal accumulation of the atmospheric oxygen concentration in the vicinity of the carboniferous period (Cu, Zn-SOD) (Berkner and Marshall 1965; Asada 1976); An explosive increase of the animal species in the sea because of the acquisition of efficient photosynthesis of carbohydrates and resultant surplus nourishment (Nakamura 1983), demanding subtle species discrimination as well as *self-non-self* (T cell evolution as the pisces propagated)

Fig. 1. Age distribution of neoplasms: Nature's evolutionary experiments on carcinogenesis. The age distribution of Fanconi's anemia was studied and compared with other cancer-prone diseases and that of the control male population of Miyagi Prefecture, Japan. Different cancer-prone diseases have different patterns of neoplastic age distribution. There is a definite tendency of *non-epithelial — epithelial tumor shift* in the control population which is taken after by the distribution pattern of Fanconi's anemia when we take it into consideration that hepatoma development is iatrogenic to the prolonged administration of androgenic steroids, resulting in an accelerated induction of the epithelial tumors. Those chromosomal injuries hitting the protooncogenes or creating novel "oncogenes" as they result from the chromosomal breakage would lead to leukemias. Accumulation of damage in, and later development of functional impairment of, the immune mechanisms would entice carcinomas. The legends for the case of Fanconi's anemia may also be implicated in other forms of the chromosomal breakage syndromes and the immunodeficiency diseases.

○, leukemias; ◊, transient leukemias; □, lymphomas; ×, BKB or brain, kidney, bone; ●, adenocarcinomas, or cancers, non-specified; ■, hepatomas; ▲, squamous cell carcinomas; •, mesenchymal; (), age not known.

(Good 1971); Further microbial and chemical contamination of the sea necessitating humoral barriers surrounding the gastrointestinal tract by dint of B cells and plasma cells (higher pisces) (Good et al. 1965; Nakamura 1983). The evolution of the immunoglobulins seems to have taken place in the order of IgM, IgG and IgA (Bellanti 1971). The evolution of the lymph nodes may bear some biological implications other than probable functional efficiency, as the event took place in the mammals (Good et al. 1965). Any defects in these defense lines if they should happen to lead to carcinogenesis can be regarded as the Nature's experiments on the merits of such selective and discrete functional aberrations.

Nature's carcinogenetic experiments in the chromosomal breakage syndromes.

TABLE 2. *Nature's evolutionary experiments on carcinogenesis*

		Impaired DNA repair (2.8 B.y.)	Decreased Cu, Zn-SOD (420 M.y.)	Immunodeficiencies				Cancer incidence			Epithelial
				T cell (500 M.y.)	B cell (350 M.y.)	L.N. (150 M.y.)	Total	Non-epithelial			
								Leuk.	Lymph.	BKB	
Males	(0-14 y.o.a.)						0.008	46	3	24	13%
(Miyagi	(15-24)	—	—	—	—	—	0.010	24	15	16	39%
Prefecture)	(25-34)						0.024	10	5	9	62%
	(35-79)						0.046	2	2	3	88%
Down's syndrome	Trisomy 21	(-)	(-)	(-)	(-)	3.7%	100%	—	—	—	—
Fanconi's syndrome	(+)	(+)	(NK cell ?)	(IgA ?)	(-)	10+	43	—	1	55%	—
Xeroderma pigmentosum	(+)	(-)	(-)	(-)	(-)	44	—	—	—	—	—
											—
Bloom's syndrome	Chromosomal instability	(-)	(+)	(-)	(-)	18.3	46 (Early)	15	8	31%	31% (Late)
Congenital X-linked (Bruton)	X-linked	—	(-)	(+)	(-)	0.7	83	17	—	—	—%
Severe combined	X-linked	—	(+)	(+)	(-)	2	33	67	—	—	—%
Common variable	—	—	(±)	(+)	(-)	8	10	56	4	29%	29%
Wiskott-Aldrich syndrome	X-linked	—	(+)	(-)	(-)	12	13	79	8	—	—%
Ataxia telangiectasia	—	—	(+)	(+)	(-)	10+	21	62	10	11%	11%
IgM deficiency	—	—	(-)	(+)	(-)	—	—	83	17	—	—%
IgA deficiency	—	—	(-)	(+)	(+)	—	—	15	16	69%	69%
Duncan's syndrome	X-linked	—	(+)	(+)	(+)	—	—	—	—	—	—
Acquired immunodeficiency syndrome (AIDS)	—	—	(+)	(-)	(+)	circ. 15%	8	58	25	8%	8%

B.y., billion years ; M.y., million years ; L.N., lymph node ; Leuk., leukemias ; Lymph., lymphomas ; BKB, brain, kidney and bone ; y.o.a., years of age.

As is seen on Table 2, Down's syndrome is characterized by the exclusive development of acute leukemias among the children (Rosner and Lee 1972) as well as the chromosomal abnormality of trisomy 21. It may be noteworthy that 21% of their own and 17% of the 276 cases of their review were diagnosed leukemic early in their newborn periods. Thus, it can be called "constitutional." The chromosome 21 seems to be closely related to hemoblastic proliferation (Mitelman 1985). According to the list, there were 11 cases of the "constitutional" leukemias, and 2 of leukemoid reactions or "transient leukemias", and their chromosome analysis revealed a variety of changes. The single trisomy 21 may not always be potent enough for maintaining the leukemic carcinogenesis, and either an intensification of the information on chromosome 21 or cooperation with chromosome 8 seems mandatory in most of the cases. The latter contains *c-myc* protooncogene that might be responsible for *immortalization* of the target cells. The protooncogene (s) to be contained in chromosome 21 can be *transforming* rather than *immortalizing* and would therefore necessitate an intensification through overdosing (double trisomy 21 or ring formation) or cooperation with *c-myc* on chromosome 8 or *erb B* and/or *mos* protooncogenes on chromosome 7 through ring formation (Benedict et al. 1979; Testa et al. 1979; Hagemeijer et al. 1981; Heaton et al. 1981; Tricot et al. 1981; Dębiec-Rychter et al. 1982; Kaneko et al. 1982; Alimena et al. 1985; Mitelman 1985). In this way, the Nature seems to have had a carcinogenetic experiment of chromosomal "disintegrative" type but without any definite viral infections superimposed on Down's syndrome.

In the cases of Xeroderma pigmentosum (XP) and Bloom's syndrome (BS), their chromosomal aberrations are yet established by the time of their birth, but are to arise and accumulate with the advancing time. Probably, the DNA damage to be incurred may not necessarily be specifically targetted, and therefore the probability of hitting the adequate protooncogenes may not be high enough. In BS, the DNA breakage by 25 years of age was seen to induce leukemias, and carcinomas after that (German et al. 1977). It is of special interest to notice that these cancers were of the gastrointestinal origin and that IgA deficiency is probable among BS, too (Pathak and Epstein 1971). In XP, however, skin cancers are rather to emerge in the young adults, but no leukemias (Robbins et al. 1974; Takebe et al. 1977).

Nature's carcinogenetic experiments in the immune defective syndromes. In such immunodeficiency syndromes, the cancer incidence rates are increased, too (Table 2). However, their contribution to carcinogenesis appears to be rather indirect. Those patients having Nezelof and DiGeorge syndromes of the purely isolated T cell deficits are likely to succumb to bacterial and viral infections before they develop any malignancies and they do not have any "constitutional" or childhood tumors. Let's look at Fig. 1 at the column ataxia telangiectasia (AT) and below. Blackened circles and triangles are to be seen limited among AT, IgA deficiency, common variable immunodeficiency and AIDS. Develop-

ment of carcinomas is confined to the older age portion of each category, and the non-epithelial tumors, to the younger generations. In addition, practically speaking, there are no leukemia cases in these categories excepting AT, one of the chromosomal breakage syndromes, and therefore, there are lymphomatous tumors only. Thirdly, the carcinomas are principally of the gastrointestinal tract. Lastly, what is common to these immunodeficiencies is the eventual IgA deficiency. Can't we simply suppose that defective anti-viral defense lines along the respiratory and gastrointestinal tracts in these patients could have enticed oncogenetic sequelae therein, and that T cell do not function by rejecting newly arising tumor cells (Moller and Moller 1978)? As they used to cherish it, the lymphomatous oncogenesis might be related to their greater probability of infections and resultant overwhelming antigenic insults (Kersey et al. 1973; Kaplan et al. 1987). In the disease status of Wiskótt-Aldrich syndrome, severe combined immunodeficiency disease, IgM deficiency and Bruton type agammaglobulinemia, the tumors are absolutely of non-epithelial categories occurring during the earliest periods of life. Then, the IgA deficiency in the case of Bruton type agammaglobulinemia may not be able to sustain these patients long enough for gastrointestinal carcinogenesis. Thus, T cell deficits are not necessarily directly carcinogenic but indirectly facilitate that kind of processes in such a way that the disease progresses along the evolutionary stratification of immunocompetency. In other words, the secretory IgA barrier can be one of the anti-carcinogenic mechanisms of evolutionary implication. The humoral immunity is essential for the defense against infections with leukemogenic viruses (Weiser et al. 1969) and probably surveillance against cancer as well. Phylogenetically, IgM appeared with the advent of the cyclostomes and IgA with the mammalian evolution (Bellanti 1971). The ontogeny of human IgM takes place during the fetal life and that of IgA after birth (Bellanti 1971). IgM is confined to the circulating blood because of its pentamer molecular size, and its primary function is to fight with invading microorganisms as it is produced as the first antibody in response to an immunogen, and it does take place even at low doses of the immunogen in good contrast to the IgG responses (Hood et al. 1978). IgA is as secretory antibody preferentially located in the gastrointestinal and respiratory tracts, and the breast (Hood et al. 1978). It may be intrigue enough to notice that with IgA deficiency, the majority of carcinomas were definitely limited to such sites that kind of immunoglobulins are expected to be on duty: 1 esophageal, 1 gastric, 3 colonic, 1 pulmonary, and 1 mammary (Kersey et al. 1973). Discrete defects of single B cell subpopulations as in the case of IgA deficiency would not necessarily fatally disable the patients (Gatti and Good 1971), but let them live longer and render them vulnerable to oncogenic viruses that much. The IgA deficiency may ensue secondarily to T cell loss as in the case of AT. Immunodeficiency is to develop rather later in life in those patients of the common variable immunodeficiency (Alexander and Good 1977). This kind of legend would well

explain the absence of leukemias during the early period of life, and the staggered incidence of lymphomas and cancers over a whole range of adult life.

Fanconi's anemia as a Nature's carcinogenetic experiments. What we originally expected of FA was a re-visualization of the phenomeon of the non-epithelial-epithelial tumor shift which is observable with the normal populations (Okuyama and Mishina 1986). You can see it in Fig. 1 if you could eliminate incidence of hepatomas which can largely be iatrogenic in one sense with the therapeutic usage of oxymetholone. An increased susceptibility of FA cells to carcinogenetic insults is well-known (Todaro et al. 1966; Sasaki and Tonomura 1973), although they did not specify if the changes were to *immortalize* or *transform* or both. The third peculiarity of FA is the absence of lymphomas throughout. And fourthly, the epithelial tumors excepting hepatomas were exclusively squamous cell carcinomas of the tongue or esophagus or female outer genitalia. There are 3 papers reporting the immunological status of FA patients: Defects in cellular immunity (Pedersen et al. 1977; Hersey et al. 1982) and IgA absence (Abels and Reed 1973). Then, the rather premature surge of the epithelial tumors in FA may possibly be related to a reduced immune surviellance with NK cells against emerging cancer cells or IgA against any viral intrusion through the gastrointestinal and female genital tracts, for NK cells are greatly and rather "selectively" sensitive to radiation and therefore to superoxide radicals, and are evolutionarily thought to have emerged prior to T and B cells (Kumagai 1985). Thus, FA may embrace the most archaic carcinogenetic defects of (1) reduced Cu, Zn-SOD contents that would lead to an increased DNA damage, (2) defective DNA repair, and possibly (3) defective NK cell immune surveillance or (4) IgA deficiency.

Evolutionary implications of Nature's carcinogenetic experiments. Carcinogenesis may be a complicated process involving the genetic material and cellular proliferation on one hand, and physical and biological intrusion on the other. In addition, *aging* as a time schedule of life should also be important. For the purpose of clarification of carcinogenesis in man, chromosomal breakage syndromes and immunodeficiencies were proven helpful especially when we tried to undo the conglomerates. The evolutionary stratification of anti-cancer strategy suggested in the present study is (i) excision repair of the damaged DNA, (ii) efficient detoxification of superoxide dismutase (Cu, Zn-SOD), and (iii) blocking of intruding viruses that are potentially leading to DNA damage over the respiratory and gastrointestinal barrier with IgA immunoglobulin. All of them have definite evolutionary dating of their own as has been described at the outset of the discussion. (iv) The lymphomatous transformation per se can be due to a compensatory proliferation and subsequent malignant transformation in any of the clones of the remaining T or B cell lines (Kersey et al. 1974). However, viral transformation may also be probable in view of the scope of the oncogenous viruses, and the definite anti-viral repertoire of the immunoglobulins: IgM

against those viruses circulating in the peripheral blood, IgG against such viral particles swarming in the interstitial space as well as in the blood, and IgA against those intruding across the mucous membrane (Alexander and Good 1977). The viral oncogenesis may be of evolutionary significance in triplicate: (1) evolutionary preservation of the protooncogenes; (2) probable "recent" evolution of the viruses relative to human beings (Matthews 1983); and (3) retroviral infectivity across the species barrier (Gallo et al. 1977). The probable strata of anti-cancer mechanisms seem to have become more legible thus far.

Naturally, statistical studies cannot help being circumstantial. However, it is sincerely hoped that the present investigations would present appropriate suggestions for any fields of cancer research. Further studies are so obviously needed.

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